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PRESENTATION OF THE HENRY JACOB BIGELOW GOLD MEDAL

INTRODUCTORY REMARKS AND PRESENTATION OF THE MEDAL*

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BOSTON

THE occasion of this meeting of the Boston Surgical Society is for the presentation of the Henry Jacob Bigelow Gold Medal. Tradition and custom, however, have decreed that some scientific contribution shall be made at every meeting of the Society. In consequence, the distinguished surgeon who will receive the Bigelow Medal, Dr. Frank H. Lahey, has been asked to present a paper. We are fortunate in that he has chosen thyroid surgery as his subject. He is well known to all in this audience and needs no further introduction. I have the honor of presenting Dr. Frank H. Lahey.

(Dr. Lahey then read a paper on thyroid surgery.)

The Boston Surgical Society was incorporated in November, 1914. In February of the following year, Dr. William Sturgis Bigelow presented the Society with the sum of five thousand dollars in memory of his father, Henry Jacob Bigelow, directing that the income derived from this sum of money be used from time to time for the presentation of a gold medal to be known as the Henry Jacob Bigelow Medal. The award is made for "new and valuable work in surgery or in fields connected with it." The medal was first awarded in 1921 to Dr. William J. Mayo. Since then eight other awards have been made, this present one being the tenth. The other recipients were Drs. William W. Keen, Rudolph Matas and Chevalier Jackson, Mr. George Grey Turner, and Drs. John M. T. Phinney, Harvey Cushing, Edward W. Archibald and Allen O. Whipple. Surgeons of the United States, England and Canada are represented.

The Society has been chary about awarding the medal to one of its own members, and it can be accepted as fact that before doing so it has interpreted the terms of the award with more than usual stringency. In consequence, only one member has previously received the medal: Dr. Harvey Cushing.

Tonight it gladly honors another member. Dr. Frank H. Lahey, director of the Lahey Clinic here in Boston, on the basis of his accomplishments not only in the field of surgery but also in those broader fields that are connected with it well merits inclusion in this distinguished group of recipients. His mastery of thyroid surgery and surgery of the esophagus and bowel, for example, is but an indication of the scope of his technical skill. The presidencies of the American Medical Association and the New England Surgical Society, the governorship of the American College of Surgeons and membership, both honorary and regular, in many other surgical societies point to his great influence among the medical profession. He has held professorial posts in Harvard and Tufts College medical schools. The Lahey Clinic is famous for the opportunities it affords for graduate studies. Without his steadying influence during the war, the civilian physician situation would have been a serious menace to the public health. Even now, his influence is being continually exerted as a member of the Presidential Advisory Committee on the Integration of Medical Services in the Government to the end that, among other things, the veterans shall receive better care.

Nor should we forget in honoring Dr. Lahey to do equal honor to Mrs. Lahey. All in this audience know what profound influence a surgeon's wife exerts on the surgeon. Without her sustaining aid his courage would many times falter; without her encouragement he would never be inspired to rise to heights believed by him to be beyond his reach. She puts up with long lonely hours, a frequently disrupted household and those temperamental peculiarities that are characteristic of a person who by nature and by training is above all things an individualist. Dr. Lahey will, I am sure, agree with me that without the devoted and loyal support given him by Mrs. Lahey he would never have achieved even a modicum of the deserved success that has been his.

Dr. Lahey — superlative surgeon, doctor who teaches doctors, redoubtable administrator, adviser of Presidents in war and peace and, above all, a man who has the courage to be honest with himself — as the representative of the Boston Surgical Society I take great personal pleasure in having the honor to present to you in its name the Henry Jacob Bigelow Gold Medal.

*This and the succeeding paper comprise the addresses delivered at the presentation of the Henry Jacob Bigelow Gold Medal at a meeting of the Boston Surgical Society, Boston, May 10, 1946.

†President, Boston Surgical Society.

SURGERY OF THE THYROID GLAND*

FRANK H. LAHEY, M.D.†

BOSTON

I HAVE selected the subject "Surgery of the Thyroid Gland" because the Lahey Clinic and I have literally grown up almost from the beginning of the developments in this field and have had a hand in bringing about some of them, because this experience represents almost as large an acquaintance with the subject as exists in the world today and has therefore made available to us a considerable knowledge of the unusual thyroid states with which men not dealing with these conditions daily are often not familiar, because it is particularly appropriate to present a review of this special experience in the community in which it has been had and to a group of surgeons with whom I have lived and who have been my friends and colleagues and, finally, because in the audience to which it is presented are many of my lay friends who I hope will be able to understand and be interested in at least more of the aspects of this review than would be true of a perhaps more erudite but less dramatic subject.

Since this presentation is in the nature of a review and a report on this experience, the material represents the work of many men in the Clinic, much of which has been published in special papers on the various individual aspects of thyroid disease. Because the subject lends itself so well to illustrative demonstration, each aspect is demonstrated, so far as possible, by illustrations, making it, I hope, additionally comprehensible to the nonprofessional portion of the audience.

This review is based on an operative experience with between 25,000 and 26,000 thyroid operations on between 22,000 and 23,000 patients with thyroid disease (Tables 1 and 2). Since this paper deals particularly with the surgical treatment of thyroid disease, no mention is made of other states that rarely require surgery, such as diffuse colloid goiter, endemic and nonendemic, thyroiditis of the Riedel's struma type and of the Hashimoto's struma lymphomatosa type, lingual goiter, sublingual goiter, thyroid tuberculosis, syphilis and abscess, unilateral absence of the thyroid gland and other nonsurgical thyroid states.

TABLE 1. *Types of Thyroid Disease.*

DISEASE	NO. OF CASES
Hyperthyroidism, including primary hyperthyroidism and adenomatous goiter with secondary hyperthyroidism	16,000
Nontoxic goiter	9,000
Total	25,000

The developments in this disease are discussed not only from the standpoint of better management in its various aspects but also to demonstrate progress in the attempt to educate the family physician, who first sees these patients, to deal with them more aggressively and at an earlier stage, before they have reached advanced degrees of emaciation and intoxication.

I have purposely selected two old photographs (Fig. 1) to demonstrate the state of intoxication to which these patients with hyperthyroidism were in the past often permitted to go, and, in the same patient, the result following subtotal thyroidectomy. This is also a graphic demonstration of what hyperthyroidism actually is. Hyperthyroidism, as can be seen from these two illustrations preoperatively and postoperatively, is a disease brought about by hypermetabolic activity, stimulated, in turn, by the excessive synthesis of thyroxine. It is now well known that the excessive synthesis of thyroxine causes the weight loss dramatically illustrated in Figure 1, which is only the external evidence of the unseen but real effects of excessive metabolism on inner, nonvisible structures, such as the liver, the heart, the epiphyseal centers in young children, the intestinal tract and the retro-ocular muscles and fat, that play a large part in intractable exophthalmos (see Figs. 7, 8, 12, 17, 18 and 19).

TABLE 2. *Mortality following Thyroidectomy.*

Number of operations	25,000
Operative mortality	0.75%
Number of patients	22,000
Patient mortality:	
All cases	0.88%
Cases since July 1, 1943	0.27%
Cases during 1945	0.17%

The introduction of iodine in the preparation of patients for subtotal thyroidectomy for hyperthyroidism, together with the improvement in technical procedures and in anesthesia and the better preoperative preparation and postoperative care of these patients, has resulted in such a lowering of mortality rates that the family physician no longer delays recommending operation until the patients have reached the states shown in Figure 1.

Thiouracil, Thiobarbital and Propylthiouracil

As the result of the development of the use of thiouracil, thiobarbital and propylthiouracil, for

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which we are greatly indebted to Dr. E. B. Astwood, no longer need surgeons fear even the seriously toxic patients with hyperthyroidism in whom, in the past, multiple-stage procedures were frequently necessary.

Because thiouracil, thiobarbital and propylthiouracil so positively and dependably bring the metabolic rate to normal in patients seriously affected by hyperthyroidism, because these dangerous but useful drugs will abolish multiple-stage procedures in the surgery of hyperthyroidism, because they will still further reduce, if not abolish the already low mortality, — a patient mortality of 0.88 and an operative mortality of 0.73 per cent, as compared with a patient mortality of 0.17 per cent with the use of these agents, — and because we have now employed these drugs in preparing for surgery over 500 patients with hyperthyroidism, it is important to report our experience with them. Because these powerful controllers of thyroid hyperactivity have real dangers, as well as real advantages, some of their complications are discussed.

Desiring to concentrate experience with these dangerous drugs in the hands of one man so that he could have the largest possible experience with them, we have turned over their administration in the preparation of patients with hyperthyroidism for surgery at the Clinic to Dr. Elmer C. Bartels. By this plan, which I recommend for any hospital using this dangerous drug in the treatment of patients with hyperthyroidism, one man, much more quickly than several men, acquires familiarity with the advantages and dangers related to the administration of this useful drug in preparing patients with hyperthyroidism for surgery.

In an article on this subject published by the Clinic,[1] a simple diagram (Fig. 2) was employed to illustrate the origin of hyperthyroidism, together with what has been suggested by many as the possible way in which these drugs bring about a return of the elevated basal metabolic rate to normal and thus abolish the symptoms of hyperthyroidism associated with the elevated metabolic rate.

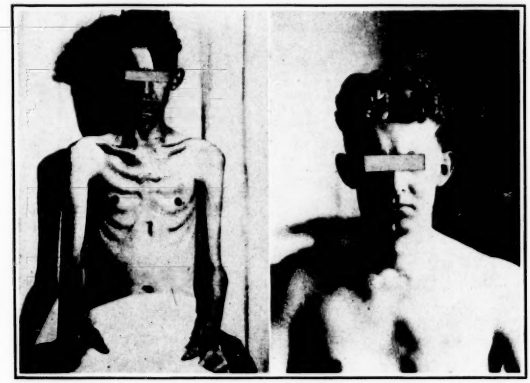

FIGURE 1. *Photographs of Patient with Severe Hyperthyroidism before and after Operation. The photograph on the left shows the extreme degree of emaciation that can result when the disease is untreated; that on the right shows the normal state that was attained after subtotal* ***thyroidectomy.***

Early in our experience in operating on patients with hyperthyroidism who had had their metabolic rates brought to normal by these drugs, we became distressingly aware of the fact that, although the patients were freed from toxicity, the thyroid glands themselves were in the same state as those before the introduction of Lugol's solution by Dr. Henry S. Plummer to prepare the patients for surgery. The thyroid glands of patients prepared with thiouracil alone were friable and vascular and did not hold double hooks; ligatures cut through, bleeding was almost uncontrollable, and microscopic section — in spite of the fact that these patients were free from toxicity — showed the glands still to be markedly hyperplastic, including all the features found in patients with severe hyperthyroidism untreated with iodine.

As may be seen in Figure 2, the effect of thiouracil, as has been suggested by many, is an extrathyroid

one, possibly on inorganic iodine, which the thyroid gland synthesizes into organic iodine, either by so affecting the iodine that it is no longer satisfactory for synthesis or by its effect on the proteolytic action of the gland so that organic iodine (thyroxine) is no longer synthesized.

If iodine is no longer synthesized into thyroxine, one can understand what Bartels[2] has observed in patients with hyperthyroidism to whom one of these three drugs had been administered: with reasonable regularity one can assume that, to bring the metabolic rate to normal, a full dosage of these drugs (0.6 gm. of thiouracil, 50 mg. of thiobarbital or from 175 to 225 mg. of propylthiouracil) will take approximately the number of days that the metabolic rate has been above normal. This finding

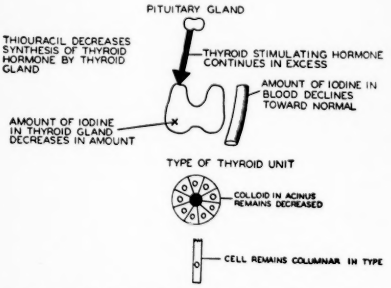
PITUITARY GLAND
THIOURACIL DECREASES SYNTHESIS OF THYROID HORMONE BY THYROID GLAND
THYROID STIMULATING HORMONE CONTINUES IN EXCESS
AMOUNT OF IODINE IN BLOOD DECLINES TOWARD NORMAL
AMOUNT OF IODINE IN THYROID GLAND DECREASES IN AMOUNT
TYPE OF THYROID UNIT
COLLOID IN ACINUS REMAINS DECREASED
CELL REMAINS COLUMNAR IN TYPE

FIGURE 2. *Physiologic Changes in Primary Hyperthyroidism following Thiouracil Therapy.*

Thiouracil brings about the return of the basal metabolic rate to normal and abolishes the symptoms of hyperthyroidism without changing the histologic picture of hyperthyroidism within the gland and without inhibiting the pituitary-stimulating hormone, which incites the hyperplasia within the thyroid (reproduced from Lahey et al.[1] by permission of the publisher).

is predicated on the reasonable basis that this period represents the time necessary to use up the thyroxine already manufactured and stored in the tissues and in the thyroid gland; it has been demonstrated that these drugs have no effect on the efficacy of thyroxine already manufactured and that their effect is only in preventing the synthesis of more thyroxine.

Figure 3 shows a high-power photomicrograph of the friable, high-columnar epithelial cells lining the acini in the hyperplasia associated with the overactive thyroid gland of hyperthyroidism untreated with iodine. This type of hyperplasia is seen in patients with hyperthyroidism whose metabolic rate has been brought to normal with thiouracil, thiobarbital or propylthiouracil and in whom, because of this persisting hyperplasia, operating conditions are unsatisfactory. Figure 4 illustrates the involution brought about in the patient shown in Figure 3 by the administration of Lugol's solution and demonstrates the dilatation of the acini and the compression of the epithelial cells lining the acini. This so-called "involution effect" brings about devascularization, firmness and almost ideal operating conditions

FIGURE 3. *High-Power Photomicrograph of the Columnar Epithelial Cells Lining the Acini.*

This is the histologic picture found in the patient with hyperthyroidism whose metabolic rate has been brought to normal with thiouracil; it demonstrates why the thiouracil-prepared thyroid gland bleeds so excessively.

in patients prepared for surgery with Lugol's solution.

Because of the undesirable operating conditions in patients with hyperthyroidism prepared solely with thiouracil, thiobarbital or propylthiouracil, Dr. Bartels and I have devised a plan combining the advantages of thiouracil and iodine. Figure 5 demonstrates the typical course, with a drop in the basal metabolic rate and a gain in weight, in a patient with hyperthyroidism during the period in which thiouracil was administered and in the final three-week period during which iodine was administered, the desirable effects of both drugs being obtained. By this means it is possible to prepare patients with severe hyperthyroidism for surgery so that ideal operating conditions are established. The metabolic rate is brought to normal, the symptoms of hyperthyroidism disappear and the gland is converted into an avascular, firmly involuted one that can be managed technically with complete satisfaction.

Table 2 presents the patient and the operative mortality in our entire series of thyroid operations,

starting with the period from our very first case and including the period when we had had relatively little experience with the disease, as well as the period before iodine was used in the preparation of the patients. The patient mortality for the entire series was reduced from 0.88 per cent on July 1, 1943, when thiouracil was first used in the Clinic, to 0.27 per cent, and the patient mortality for the year 1945 was but 0.17 per cent, representing a patient who died of coronary disease. During this period no multiple-stage operations were performed. The average stay in the hospital has decreased from fifty-five days in patients prepared with iodine who required three-stage operations and thirty-five days in patients prepared with iodine who required two-stage operations to eight days in patients prepared with one of these three drugs.

FIGURE 4. *Low-Power Photomicrograph of Thyroid Gland. This demonstrates involution brought about by the intrathyroid effect of iodine and shows the dilatation of the acini, the compression of the epithelial cells lining the acini and the production of firmness and devascularization, which furnish ideal operating conditions.*

In 100 patients with severe hyperthyroidism treated with one of these three drugs, Bartels[2] has shown that the average basal metabolic rate was +49 per cent before treatment and +7 per cent after treatment and that the average weight loss before treatment was 25 pounds and the average weight gain after treatment, 12 pounds.

Complications occurring with the administration of these drugs can be — and have been — of a serious character. They consist of various degrees of neutropenia and granulocytopenia, fever, skin eruptions and enlargement of the salivary glands. Dr. Bartels has demonstrated that these complications can be anticipated in 9 per cent of patients treated with thiouracil and in 28 per cent of patients treated with thiobarbital. We have now operated on 60 patients prepared with propylthiouracil, with 100 others in preparation for surgery. Propylthiouracil has not as yet been employed long enough and in large enough doses to be certain of its complications. Two patients have already shown marked depressions of the white-cell count; in 1, the white-cell count was reduced to 1900, with no neutrophils. We strongly suspect that although propylthiouracil may produce fewer complications than the other two drugs, it will prove capable of causing death if given in doses adequate to reduce the metabolic rate to normal (equivalent to 0.6 gm. of thiouracil).

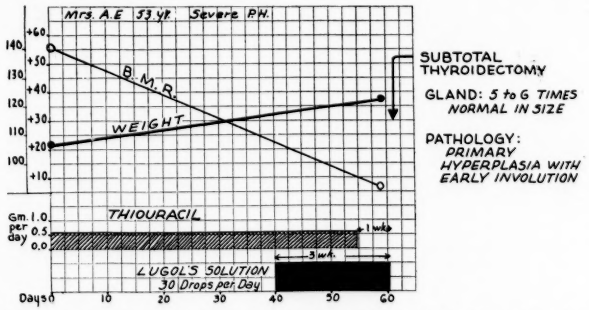

FIGURE 5. *A Plan for the Preoperative Preparation of Patients with Hyperthyroidism by the Combined Use of Thiouracil, Thiobarbital or Propylthiouracil and Iodine.*

It should be noted that Lugol's solution is given during the last three weeks of preparation, bringing about involution and ideal operating conditions. No thiouracil is given for the last week before operation because of the fact that agranulocytosis has occasionally been found to occur as late as seven days after the last dose of such drugs, a complication that would be undesirable either at the time of operation or during postoperative recovery (reproduced from Bartels[2] by permission of the publisher).

Dr. Bartels has demonstrated that if these complications occur and the drugs are stopped and again administered, there will be an increased hazard of recurrence. He has also shown that agranulocytosis and neutropenia can occur up to seven or eight days after withdrawing the drug and as late as the ninth month after beginning treatment and on a dose as low as 0.2 gm. of thiouracil. It is for these reasons that no thiouracil, thiobarbital or propylthiouracil is given for a week before the patient comes to operation (Fig. 5), to avoid the coincidental occurrence of one of these states with the operative procedure or postoperative recovery.

When agranulocytosis and neutropenia — the most dangerous of all these complications — have occurred, no treatment can compare in usefulness with that of penicillin in large doses. Pyridoxine, vitamin B-6 and liver extract are administered together with penicillin, but penicillin is the single measure on which the greatest dependence can be placed.

These patients are kept under close observation, with frequent white-cell and differential counts, and

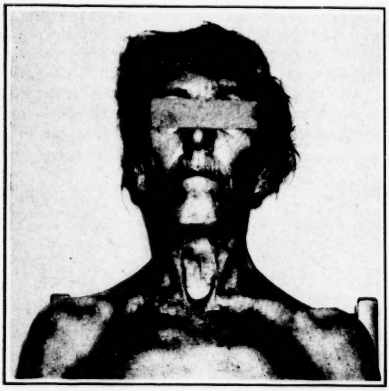

FIGURE 6. *Typical Activated Hyperthyroidism. This should be compared with Figure 7, which shows typical apathetic hyperthyroidism.*

on the appearance of any real depression of either the white cells or the granulocytes, the drug is immediately withdrawn.

The final question regarding the employment of these three drugs is, Will it be possible by the use of one of them to eliminate the necessity for operation? Can the metabolism be maintained at a normal level over a long period, so that a persisting remission can be accomplished? This question cannot be definitely answered at present. It can be answered only after a larger experience over a long period. At present, it is Dr. Bartels's experience that in patients with small thyroid glands who have had the disease for a short time, remissions may be accomplished. How long they will last, no one as yet knows. In patients who have had the disease a long time and with large glands, recurrences will follow the withdrawal of the drug in a large percentage of cases.

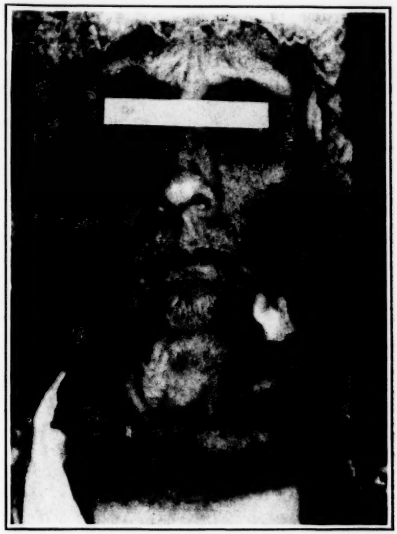

FIGURE 7. *Typical Apathetic Hyperthyroidism. Note the lack of activation and thyroid enlargement and the wrinkled and pigmented skin.*

Of these three drugs it appears reasonable to say that, at least so far, propylthiouracil appears to possess less danger of the complications that occur with thiouracil and thiobarbital, but 's not free from danger, that these drugs, particularly thiouracil and thiobarbital, unless administered by one familiar with their use, will produce mortality rates as high as, if not higher than, that following expert surgery. In experienced hands, however, they will eliminate multiple-stage procedures and largely abolish the mortality of subtotal thyroidectomy. They will find their greatest usefulness in patients with hyperthyroidism with complicating states, such as diabetes, pregnancy and cardiac decompensation.

Apathetic Hyperthyroidism

Because a chronic type of hyperthyroidism of low grade that frequently occurs in older people, to which I gave the name "apathetic hyperthyroidism" some years ago, is often overlooked, being different from the typical activated hyperthyroidism shown in Figure 6, I call attention to the existence of this atypical type, illustrated in Figure 7.

I gave the name apathetic hyperthyroidism to this condition, not with any idea that it represented any special group but merely to call attention to the fact that there is a type of hyperthyroidism without eye signs, without activation, without marked enlargement of the gland and with only moderate tachycardia but particularly associated with marked weight loss and marked myasthenia over a long period and that because of the lack of these outstanding signs this type of hyperthyroidism is often overlooked. I also called attention to the fact several years ago that this type of hyperthyroidism, which is frequently associated with only moderate elevations in basal metabolic rates, is often approached too confidently by the surgeon because it does not have striking signs of overactivation; the condition is not given the attention and caution warranted by the reactions and fatalities that can occur following surgery in this type of hyperthyroidism.

I am sure, as I have repeatedly written, that there are many patients with such a low grade of this type of chronic hyperthyroidism, exhibiting such unstriking evidences of disease, who are undiagnosed in many communities. It is in these patients that proper preoperative preparation and subtotal thyroidectomy can achieve some of the most brilliant results in the surgery of hyperthyroidism.

Thyrocardiac Disease

Figure 8 shows a preoperative and postoperative view of a patient belonging in the group of thyroid conditions to which Hamilton and I[3] gave the name thyrocardiac. It was with Dr. Hamilton's aid and encouragement that I began our early surgical treatment of patients with cardiac failure, brought about by an associated hyperthyroidism.

Figure 9 graphically demonstrates why cardiac decompensation occurs in patients with hyperthyroidism.[4] It will be noted in this diagram, devised by Dr. Hurxthal, that in the patients with any limited cardiac capacity, the superimposed needs of increased circulation rate associated with an increased metabolic rate cannot be met by a compensatory increase of the circulation rate with an inadequately capable heart; the section illustrating the high metabolic rate with only a normal uncompensating circulation rate demonstrates why failure occurs and how it is possible, by means of subtotal thyroidectomy, which brings the metabolic rate to normal, or by means of the administration of thiouracil, thiobarbital or propylthiouracil, which brings the metabolism to normal, to bring the circulation rate and metabolic rate into balance, with restoration of compensation. Figure 10 shows the cardiac shadow in a thyrocardiac with failure and the return of the cardiac shadow to normal following the elimination of the hyperthyroidism by subtotal thyroidectomy as graphic evidence of this accomplishment.

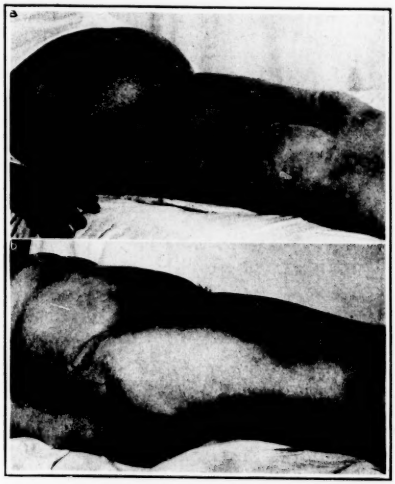

FIGURE 8. *Photographs of a Thyrocardiac Patient before and after Subtotal Thyroidectomy.*

Before operation (a) *there were anasarca and ascites. After operation* (b) *there were restoration of compensation and relief from hyperthyroidism.*

TABLE 3. *Follow-up Data in 614 Patients Operated on for Thyrocardiac Disease (1922-1941).*

Patient untraced		143
Patient dead		165
Patient alive:		
Grade I result	201	
Grade II result	100	
Grade III result	5	
	306	

Table 3 presents the number of patients, of a total of 306 known to be living, who have obtained Grade I, Grade II and Grade III results among those who have been followed postoperatively for varying periods from 1922 to 1941. Grade I repre-

sents a perfect result, with no return of decompensation, no myxedema, auricular fibrillation or perfailure. Again, the name "thyrocardiac" was given to these cases not because they represent an unusual

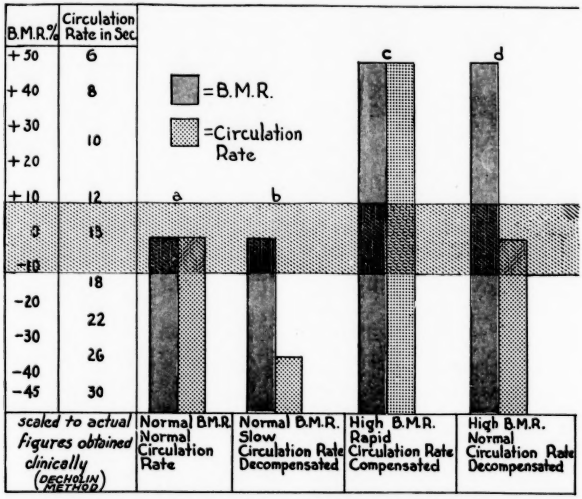

FIGURE 9. *The Relation of Circulation Rate to Heart Failure. With a normal basal metabolic rate and a slow circulation rate* (b) *cardiac decompensation results; with a high basal metabolic rate and a high circulation rate* (c) *there is no failure; with a high basal metabolic rate and a normal circulation rate* (d), *incapable of being compensatorily elevated, the heart becomes decompensated. The last represents the state in the thyrocardiac patient (reproduced from Lahey et al.[4] by permission of the publisher).*

sisting hyperthyroidism, Grade II a perfect result so far as no return of cardiac failure is concerned

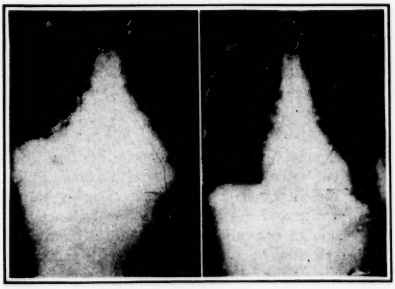

FIGURE 10. *Roentgenograms Showing the Change in the Size of the Heart Shadow following Subtotal Thyroidectomy. With return of the basal metabolic rate to normal, the circulation rate matches the cardiac capacity and compensation is restored.*

but with myxedema or persistence of some hyperthyroidism, and Grade III a return of cardiac or extraordinary group but to call attention to the hopefulness of restoring cardiac compensation with

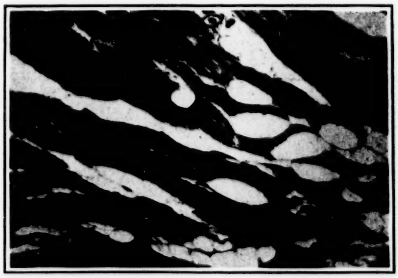

FIGURE 11. *Photomicrograph of a Section of Skeletal Muscle from a Patient with Severe Hyperthyroidism. Note the histologic signs of true muscular dystrophy.*

a high prospect of permanent maintenance in a group of patients otherwise doomed to death or disability because of the fact that decompensation cannot be restored until the load imposed on the heart by hyperthyroidism is eliminated.

Myasthenia

Over the years, everyone who has dealt with patients afflicted with hyperthyroidism has been conscious of the frequency with which myasthenia has been associated with the disease and with the fact that, with relief of the hyperthyroidism, there is complete disappearance of the myasthenia.

Many years ago Dr. Henry S. Plummer called attention to the association of quadriceps weakness with this disease and devised a chair-standing test by means of which a patient must step on a chair, thus demonstrating his degree of quadriceps weakness. Several years ago I devised a straight-leg test to demonstrate that, owing to quadriceps weakness,

FIGURE 12. *Photographs of a Patient with Severe Hyperthyroidism before and after Subtotal Thyroidectomy. Note the effect of severe hyperthyroidism on the muscles of the hands and the improvement following complete relief of hyperthyroidism by operation.*

FIGURE 13. *Advanced Intractable Exophthalmos of the Left Eye.*
The left eye was enucleated, but the right eye was saved by unroofing the bony orbit by the plan shown in subsequent illustrations. Had it been possible to deal with the left eye at the same stage as the right eye in this illustration, both eyes could have been saved by this procedure.

a patient with hyperthyroidism, sitting in a chair, could not hold his leg out straight as long as a normal person could.

It is of interest to note that Dr. Bartels has demonstrated by means of muscle biopsies that this is a true muscular dystrophy (Fig. 11). Figure 12 illustrates the change in the muscular state of the hands of a patient with hyperthyroidism preoperatively and postoperatively. As stated above, this is one of the real but unappreciated effects of the excessive metabolism in patients with hyperthyroidism who are permitted to remain untreated for a long time.

FIGURE 14. *Intractable Exophthalmos with Increasing Lid Pressure.*
The photograph on the right shows the relief from pressure obtained following unroofing of both bony orbital canals (reproduced from Poppen[6] by permission of the publisher).

Exophthalmos

It has always been of interest to me to present some of our experiences with intractable exophthalmos because I am sure, except in a group that deals with thyroid disease in large numbers, that many men go through an entire medical lifetime without having to deal with such a case. Because any day such a case may arise in anyone's experience, I wish to present the dangers that occur in intractable exophthalmos and the measures that may be undertaken to prevent the loss of eyes in these patients.

It is important to remember that intractable exophthalmos is more frequently associated with myxedema, either postoperative, spontaneous or as a result of thyroiditis, than with hyperthyroidism. Figure 13 presents an example of an intractable exophthalmos in which the left eye was needlessly lost and could have been saved, as was the right eye, had the condition been properly dealt with earlier.

Exophthalmos was shown by Naffziger[5] to be the result of a myxomatous infiltration of the ocular

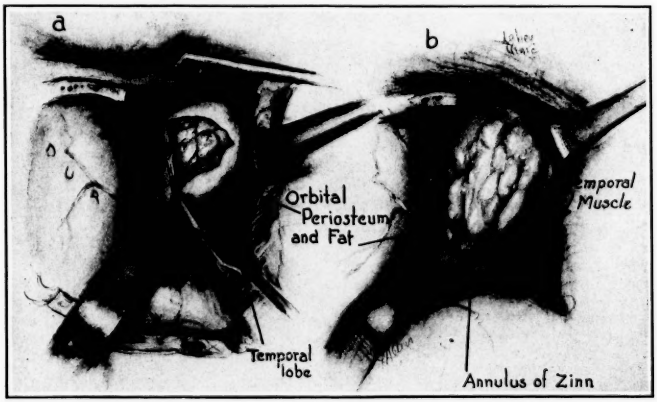

FIGURE 15. *Steps in the Operation for Intractable Exophthalmos.*
In a, *through a parietal flap with the frontal lobe elevated, the bony roof of the orbit has been rongeured away and the incised orbital periosteum and the underlying fat are seen; in* b *there is upward bulging of retro-ocular fat and muscles, with relief of forward pressure on the eye.*

muscles and the retro-orbital fat, resulting in edematous enlargement of the muscles and infiltration of the retro-ocular fat and thus crowding the eye forward and producing lid pressure on the conjunctiva, with consequent loss of nutrition and with ulceration and infection (Fig. 13).

Up to ten years ago, we had seen eyes lost in 6 cases as the result of this condition. Since the employment of the Naffziger operation by the neurosurgeons of the Clinic, Drs. Gilbert Horrax and James L. Poppen, no eyes have been lost in patients with intractable exophthalmos.[6] Because the periosteum of the orbit. There is a bulging of the retro-orbital fat as soon as the periosteal covering over the orbital canal is opened. Figure 16 illustrates diagrammatically the anatomy of the orbital canal, the segment of orbital plate to be removed, the bulging of ocular muscles and retro-orbital fat through the decompressed, unroofed, orbital cavity and the projection of the eye preoperatively and its recession following decompression.

Although this operation, devised by Naffziger, will not abolish in many of the cases the unsightly

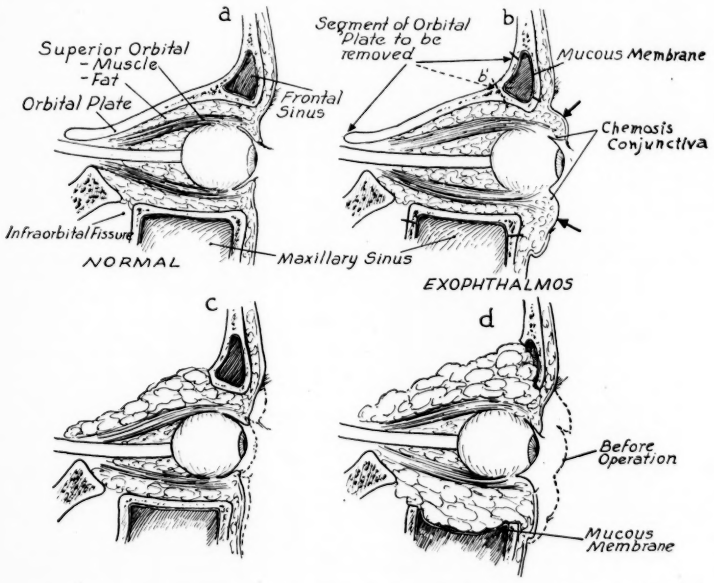

FIGURE 16. *Diagrams Representing the Various Steps in Decompression of the Eyeball in Intractable Exophthalmos.*

of the serious danger to the eyes in patients with extreme exophthalmos I wish particularly to urge that, should there be any evidences of lid pressure, as shown in Figure 14, which illustrates the preoperative state and postoperative result in such a case, prompt measures should be undertaken by means of orbital decompression to relieve this pressure. Figure 15 demonstrates the method of decompressing the orbital canal. After exposure, the parietal bone flap is turned down, the frontal lobe of the brain is turned up, the bony roof of the orbit is rongeured away and an incision is made in exophthalmos, it will, if done in time, prevent ulceration, infection and, if loss of blood supply has not already taken place, save the eye. It will obviously be of no value, however, to patients who are sent for management at the stage shown in the left eye in Figure 13.

Liver Function

In addition to the external results of the advanced stage of hyperthyroidism shown in Figure 1, serious nonvisible and often unappreciated effects are going

on at the same time, among which depression of liver function pre-eminently causes death.

Figure 17 illustrates the effect, as determined by Bartels,[7] on the glycogenic function of the liver as demonstrated by hippuric acid excretion in relation

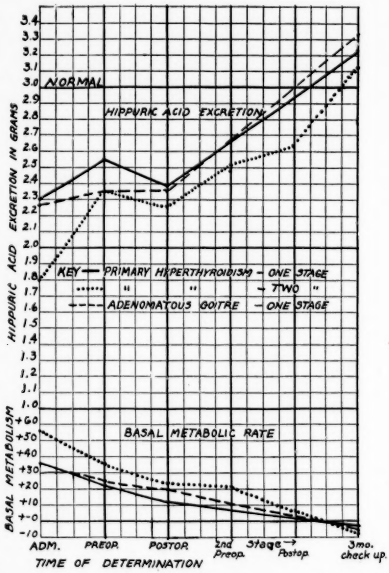

FIGURE 17. *Hippuric Acid Excretion and Basal Metabolic Rate in Hyperthyroidism.*

This chart shows the effect on liver function, as determined by hippuric acid excretion, in patients with three types of hyperthyroidism. Note the relation of the depression of hippuric acid excretion to the elevation of the basal metabolic rate, and the return of both to normal following operation (reproduced from Bartels[7] by permission of the publisher).

to the severity of the disease in the three groups and grades of hyperthyroidism, as well as the return of the glycogenic function to normal with the return of the metabolic rate to normal. It is to be noted that the degree of depression of this glycogenic function of the liver is quite accurately related to the depression of the metabolism and to the return to normal of the basal metabolic rate following subtotal thyroidectomy.

Figure 18 shows the correlated effects on serum albumin and total serum protein preoperatively and postoperatively following the restoration of the basal metabolic rate to a normal level in patients with hyperthyroidism.

It is of value to present these graphic illustrations of the unseen effects of hyperthyroidism on patients who are permitted to maintain high basal metabolic rates over long periods, because of their relation to mortality. I have often observed in the past years, after having seen many patients die of hyperthyroidism before any operation could be performed, that thyroid deaths, associated with hyperthermia and jaundice, were more frequently the result of diminished liver function than that of the excessive metabolism on any other single structure in the body.

Lipocaic in the Diarrhea of Hyperthyroidism

Owing to the fact, as stated above, that family physicians and patients are less fearful of surgical

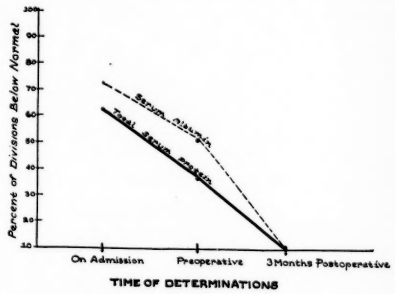

FIGURE 18. *Percentage of Serum Albumin and Total Protein Levels below Normal before and after Operation.*

This chart demonstrates the effect of hyperthyroidism on the proteogenic function of the liver.

procedures for hyperthyroidism than they were in past years, few patients now present themselves to us for care in a state of thyroid crisis. Occasional patients, however, are still sent to the Clinic for management in a state of crisis, and among the conditions making these states most difficult to deal with is that of the diarrhea associated with hyperthyroidism. Bartels,[8] who has been interested in this subject, has listed the possible causes of diarrhea in hyperthyroidism, one of the most probable of which is altered pancreatic secretion, which is known to exist in severe states of hyperthyroidism (Table 4).

TABLE 4. *Possible Causes of Diarrhea in Hyperthyroidism.*

HYPERMOTILITY
Direct action of thyroid secretion on the intestinal musculature
Vagal stimulation by thyroid excretion
Reduction in gastric acids
Retarded intestinal absorption (primary or secondary)
Altered pancreatic secretion
Reduced hepatic function
Altered adrenal function

Figure 19 demonstrates the effects of the administration of lipocaic to such a patient in crisis,

with sixteen movements daily. It is to be noted, as has been our experience and that of many others, that following the administration of this material there is prompt control of the diarrhea.

Lipocaic is a product of the alpha cells of the pancreas, proposed by Dragstedt,[9] of Chicago, and

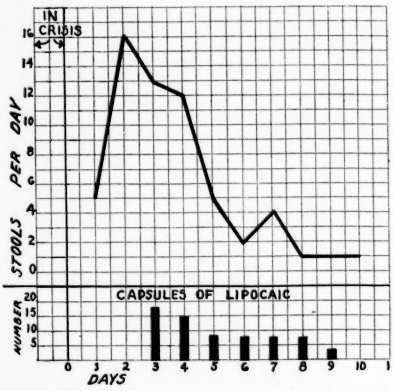

FIGURE 19. *The Effect of Lipocaic on the Diarrhea associated with Hyperthyroidism.*

Note the return to a normal number of bowel movements within a week following the administration of this material (reproduced from Bartels[8] by permission of the publisher).

has to do with fat metabolism. It has proved to be of great value in controlling the undesirable diarrheas often associated with thyroid crises, which make it

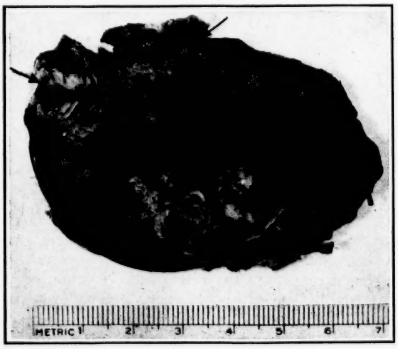

FIGURE 20. *Photograph of a Specimen Showing the Origin of a Carcinoma within an Adenoma of the Thyroid Gland.*

Note the complete erosion of the capsule between the two arrows, where the centrally originating carcinoma has extended to involve the parenchyma (reproduced from Lahey, Hare, and Warren[10] by permission of the publisher).

impossible to manage these patients so long as such a large fluid and fuel loss continues.

Cancer of the Thyroid

Cancer of the thyroid used to be considered a particularly depressing aspect of thyroid disease. This was largely because patients with this lesion were often not seen until extensive malignant processes involved the entire neck, with large, nodular and fixed masses.

To approach this subject from the proper point of view, it should be realized that practically all

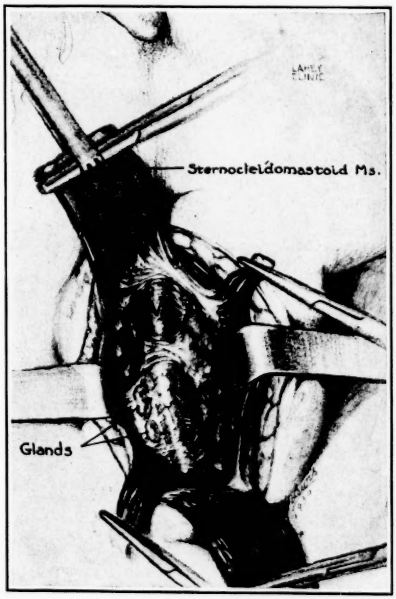

FIGURE 21. *A Drawing of Typical Lateral Aberrant Thyroid Masses.*

Note their glandlike structure and their location running up and down laterally to the internal jugular vein.

thyroid cancers originate from two sources — fetal or embryonal adenomas (Fig. 20) and aberrant thyroid glands (Fig. 21). For practical purposes, nearly all thyroid cancer originates in a previously existing benign, true adenoma of the gland, the percentage of malignancy being greater in fetal or embryonal adenomas than in the true, fully differentiated adenomas. Figure 20 shows a cancer arising within the capsule of a thyroid adenoma, with invasion and destruction of the capsule. Graham,[11, 12] a number of years ago, demonstrated that so long as the cancer is within the fibrous capsule of the adenoma there will be but rare metastases to lymph

nodes, such metastases as occur being of blood-borne variety, but that as soon as the growth has eroded the capsule and involved the true parenchyma of the thyroid gland, with its rich supply of lymphatics, early lymph-node metastases will ensue. This illustration is presented to re-emphasize that the best approach to the treatment of cancer of the thyroid gland — in spite of the fact that the incidence of malignant degeneration within these

Dr. Ficarra and I[18] reported the experience in the Clinic with 47 patients with lateral aberrant thyroid glands in which the tissue on removal showed papillary adenocarcinoma so frequently that I strongly believe that all lateral aberrant thyroid glands should be considered potentially cancerous.

Table 5 demonstrates that this type of cancer is of a relatively low grade since but two of the patients died of carcinoma. It is to be noted, however, that

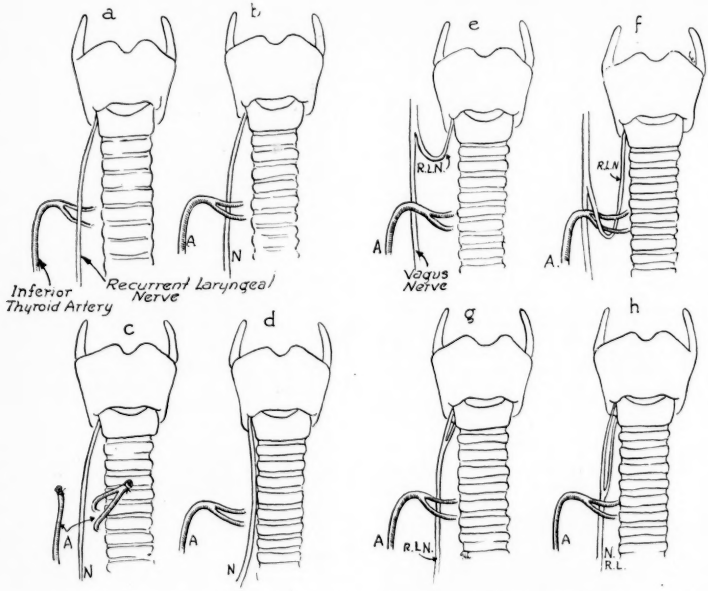

FIGURE 22. *The Various Normal and Abnormal Positions of the Recurrent Laryngeal Nerve (reproduced from Lahey[15] by permission of the publisher).*

adenomas is relatively small, perhaps not over 5 per cent — is to remove all discrete adenomas before they have become malignant or if they have become malignant, before the capsule of the adenoma has been eroded. Although a change in consistence, such as increasing firmness or increasing fixation, is an indication of possible malignant degeneration within these adenomas, I am convinced that all discrete adenomas, since their removal is not associated with any mortality, should be removed as soon as they are discovered and before malignant degeneration has taken place.

Figure 21 presents an example of lateral aberrant thyroid glands. In a recent article on this subject, 6 patients had recurrences, required reoperation and are well and that 3 are living with recurrences, one of whom has pulmonary metastases.

Lateral aberrant thyroid glands, originating as they do in the ultimobranchial bodies from the fourth pharyngeal pouch, are located as lateral glandlike tumors running up and down in front of and in relation to the sternomastoid muscle and internal jugular vein (Fig. 21). They may be multiple glandlike structures or a single large tumor mass. They should, in our opinion, all be removed radically, and when on pathological section they prove to be papillary adenocarcinomas, they should be treated radically by block dissection of the neck,

consisting of removal of the entire internal jugular vein from the mastoid to the clavicle, together with the entire front half of the sternomastoid muscle, all the adjacent lymph nodes and all the thyroid lobe on that side.

It is important in these cases to remove the thyroid lobe on the same side when papillary adenocarcinoma occurs in lateral aberrant glands because fusion between the aberrant gland originating in the

TABLE 5. *Data in 47 Cases with Lateral Aberrant Thyroid Glands.*

CONDITION OF PATIENT	CASES BEFORE 1939	CASES SINCE 1939
No recurrence	20	13
Reoperation for recurrence; patient well	5	1
Patient living with recurrence	3*	0
Death from recurrent cancer	2	0
Operation too recent for evaluation	0	3
Total	30	17

*One patient has pulmonary metastases.

ultimobranchial bodies with the true gland often results in the inclusion of malignant degeneration within the associated lobe of the thyroid gland itself. This probably explains why in these cases papilliferous aberrant thyroid nodules similar to those lateral to the thyroid gland are occasionally found within the substance of the thyroid gland.

Table 6 presents a five-year follow-up study of 231 patients with cancer of the thyroid gland, in-

TABLE 6. *Five-Year Survival in 231 Cases of Carcinoma of the Thyroid Gland.*

TYPE OF CARCINOMA	SURVIVAL %
Adenoma, with blood-vessel invasion	71
Papillary cystadenoma, malignant	62
Papillary adenocarcinoma	80
Alveolar adenocarcinoma	27
Small-cell carcinoma	22
Giant-cell carcinoma	17
Fibrosarcoma	33

cluding the different types of malignancy, with their five-year survival rates.[1] As will be seen from these figures, which represent the treatment of thyroid cancer by radical removal followed by intensive irradiation, this condition is by no means as hopeless as it was formerly thought to be.

Recurrent-Nerve Paralysis and Preservation of Parathyroid Glands

Some years ago I[14] suggested that the recurrent laryngeal nerve be dissected and demonstrated in every patient operated on for thyroid disease. Figure 22 demonstrates the usual and the unusual positions of the recurrent laryngeal nerve. It shows the relation of the nerve to the inferior thyroid artery, either before or behind it (*a* and *b*), the methods of exposing the nerve when it is behind the artery by severing the artery (*c*), and its fusion with the trachea in intrathoracic goiter from being pressed against the trachea (*d*). The recurrent laryngeal nerve often does not descend into the larynx but crosses from the vagus directly into the larynx (*e*) or descends as far as the inferior thyroid and then ascends to enter the larynx (*f*). There are two different types of extralaryngeal division of the recurrent laryngeal nerve into its adductor and abductor fibers (*g* and *h*).

It has been taught to every surgeon in the Clinic that exposure of the recurrent laryngeal nerve, which is not difficult, not only adds to the preservation of the vocal-cord innervation by avoiding injury

FIGURE 23. *Roentgenogram of a Large Intrathoracic Goiter. Obviously this intrathoracic mass could not have been made to pass through the upper thoracic strait. It is in this type of intrathoracic goiter that breaking down the center of the goiter to collapse it makes it possible to deliver the mass without removing a portion of the chest wall or the clavicle.*

to the nerve but also, because the complete anatomy of the thyroid gland is exposed, permits more radical removal of thyroid tissue, since one knows where the nerve and the parathyroid glands are and can thus avoid leaving behind large sections of the gland to protect these structures, as when the nerves are not demonstrated and visualized.

The technical step of demonstration of the inferior thyroid artery and the recurrent laryngeal nerve has in addition made it possible to find in

practically every patient operated on for thyroid disease in the Clinic at least two parathyroid glands. It is now our belief that practically no thyroid operation should be done in which it cannot be demonstrated that two parathyroid glands with a good blood supply have been preserved, thus avoiding the possibility of one of the most undesirable complications that occasionally occur with subtotal thyroidectomy for hyperthyroidism — that is, tetany.

FIGURE 24. *Photograph of a Large Extrathoracic and Intrathoracic Goiter.*

The small portion above is the extrathoracic goiter, and the large mass below the intrathoracic goiter (see Fig. 25).

Paralysis of the recurrent laryngeal nerve is not serious when but one nerve is injured, since the vocal cords on the uninjured side will overcompensate to provide a reasonably good voice, and there will usually remain a reasonably adequate glottic space for breathing. When, however, both recurrent laryngeal nerves are injured, eventual fibrosis of the vocal cords, together with arytenoid fixation, results in such a narrowing of the glottic space that there is an inadequate airway for the intake of a sufficient amount of oxygen to meet the demands of only moderate physical activity. It has, therefore, proved worth while in this large experience with thyroid operations to dissect and expose every recurrent laryngeal nerve in every patient operated on in the Clinic for thyroid disease, to be certain that the nerves are preserved.

Intrathoracic Goiter

Figure 23 illustrates a typical, large, intrathoracic goiter. Figure 24 shows the specimen of such an intrathoracic goiter after removal, and Figure 25 the deviation of the trachea in such an intrathoracic goiter. Figure 26 demonstrates the compression effect on the trachea, resulting in diminution in caliber to a half in such an intrathoracic goiter. In Figure 27 is shown an infrared photograph of a patient before the removal of a large intrathoracic goiter to demonstrate the effect on compensatory venous circulation in the superficial thoracic veins brought about by the pressure of an intrathoracic goiter on the internal jugular veins, interfering with the return venous flow from the head. One should note the enormous dilatation of the superficial thoracic veins as compared with the normal superficial thoracic venous circulation.

FIGURE 25. *The Effect on the Trachea of a Large Intrathoracic Goiter.*

Note the marked forward deviation of the trachea.

When one considers the diameter of such an intrathoracic goiter, it becomes obvious that such an intrathoracic tumor cannot be made to pass through the upper thoracic strait because its diameter is so much greater than that of the strait. It is in such

cases that I wish particularly to call attention to the fact that it is not necessary to remove ribs or the clavicle in an attempt to enlarge the upper thoracic aperture so that an intrathoracic tumor of this diameter can be made to pass through it. By ligating the superior and inferior thyroid arteries, together with the venous connections of the thyroid to the internal jugular vein, it is possible completely to devascularize this intrathoracic tumor, and to make an incision into the capsule, insert a finger into the center of the semisoft mass, break its center down, suck out its semiliquid contents, separate its capsule from the surrounding pleura and gradually deliver the entire tumor through the upper thoracic strait without enlarging that aperture.

In Figure 26, in which the caliber of the trachea has been reduced to approximately one third the normal size by the pressure of the intrathoracic goiter, it can be demonstrated how necessary it is, before an attempt is made to remove such an intrathoracic goiter from the chest, to introduce a rigid-walled, flexible intratracheal tube into the trachea under direct laryngoscopy so that the manipulations necessary for the removal of such an intrathoracic goiter do not result in compression of the trachea and produce such interference with respiration and anesthesia that they cannot be maintained.

A great many patients have been operated on in the Clinic with completely intrathoracic goiters large enough to require extensive manipulative measures within the thorax in which the compression of the trachea has been of such extent that an intratracheal tube could not be introduced under a general anesthesia; such an anesthesia would have resulted in choking from closing of the small remaining tracheal airway. In such cases it has been possible for our anesthetists to introduce the intratracheal

FIGURE 26. *The Compression Effect on the Trachea of a Large Intrathoracic Goiter. Note the reduction of the caliber of the trachea to one half to one third its normal size.*

tube first into the cocainized larynx and then to induce general anesthesia safely.

It is to be noted that the effect of an intrathoracic goiter is not only one of pressure on the trachea to interfere with breathing but also one of pressure on the internal jugular veins, increasing intracranial venous pressure and interfering with the return of venous flow from the head and neck.

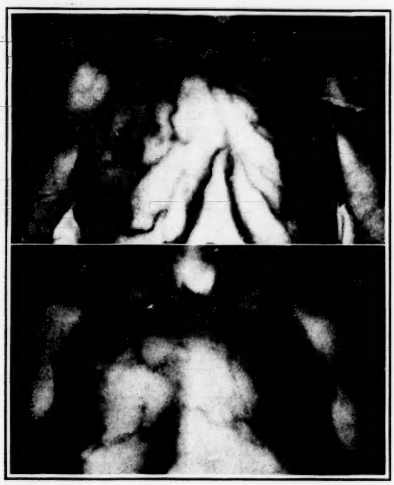

FIGURE 27. *Infrared Photographs of a Patient with an Intrathoracic Goiter before and after Removal.*

Note the enormous compensatory dilatation of the superficial thoracic veins previous to the removal of the intrathoracic goiter (upper photograph) as compared with normal superficial thoracic venous circulation after operation (lower photograph).

Before leaving this subject I wish particularly to call attention to the fact that in any patient in whom a previously obvious thyroid tumor in the neck has disappeared one should seriously consider the possibility that it has descended into the superior mediastinum, that an adenomatous goiter whose lower pole cannot be felt should seriously be considered to have become intrathoracic, and that in any patient with a large intrathoracic goiter disappearing beneath the clavicle, x-ray films should be taken particularly directed toward demonstrating the trachea to determine whether or not there is deviation of the trachea by an intrathoracic goiter and an extension of the goiter into the mediastinum.

Finally, all adenomatous enlargements of the thyroid gland that tend to extend beneath the clavicle should be removed before they become intrathoracic goiters of such magnitude as those illustrated in Figures 23, 24 and 25.

* * *

This paper represents a review of thirty years' experience with the surgery of the thyroid gland. In it are discussed some of the newer developments and some of the less frequent complications of thyroid disease as seen in a clinic dealing with these states in large numbers of cases.

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CLINICAL NOTES

VISCERAL LEISHMANIASIS*

Report of a Case

Sydney P. Waud, M.D.,† and Sam Kruger, M.D.‡

HINES, ILLINOIS

VISCERAL leishmaniasis (kala-azar) in American personnel returning to the United States has been rare. Burchenal and Woods§ reported 3 cases in American troops who had contracted the disease in the Mediterranean area. It is estimated that approximately 60 cases of the disease have occurred in American troops during World War II, the majority of which were contracted in the India-Burma Theater. The endemic areas where American personnel have been stationed are India, North Africa, Sicily, Southern Italy, Manchuria and China.

Visceral leishmaniasis is an infective disease that is characterized by fever, splenomegaly and usually hepatomegaly, as well as by a loss of weight and leukopenia, generally running a chronic course. Since the incubation period varies from six days to six months and since the course of the disease may last a year and a half, the total time from the inception to the termination of the disease is approximately two years. This is definitely of importance, since the soldier may have time to become a civilian and manifest the symptoms of the disease long after his return to the United States.

It is believed that this disease is worthy of attention because, if untreated, it is fatal in 90 per cent of cases, whereas prompt diagnosis and treatment ensure recovery in approximately 95 per cent.

K. P., a 22-year-old veteran, was admitted to the hospital on February 8, 1946, complaining of chills, fever and a mild headache. The patient had been stationed in and around Calcutta, India, for 2 years and had returned to the United States in December, 1945. He had not been on suppressive quinacrine (Atabrine) therapy and had not had malaria. There was nothing of significance in the family history, all members of the immediate family being well. The patient himself had been well until the onset of the present illness, which had begun during the 3rd week in December, while he was en route home from India. He noticed at first a chilliness followed by a slight fever every evening. He stated that he had reported to the sick bay, where he was treated for an upper respiratory infection. After arrival in the United States he was discharged from the Army; apparently, little or no evidence of the illness was present at that time, and the final Army physical examination was negative. The patient stated that the symptoms increased somewhat in severity on about January 1, but that he still did not feel sick enough to consult a physician. In the middle of January, however, at his mother's insistence, he consulted a physician. The patient was placed on bed rest and given a high-calorie diet and some medication, which he believed to be a "tonic." All symptoms gradually subsided, and the patient felt well enough to make a trip away from home. Early in February, however, there was an exacerbation of symptoms, and actual chills, with high temperatures, occurred. Occasional, mild headaches were also noted. The patient stated that he had lost about 15 pounds since the onset of the illness.

Physical examination revealed a poorly developed and poorly nourished man, who did not appear acutely ill. The temperature was 104°F., the pulse 126, and the respirations 24. The blood pressure was 110/75. The head was of normal configuration. The scalp, ears, eyes and nose were normal. There was a fine tremor of the tongue. The pharynx was not injected. There was no cervical adenopathy and no stiffness or other abnormality of the neck. The thyroid gland was not palpable. The chest was symmetrical, with prominent costochondral junctions. Tactile fremitus, resonance and breath sounds were normal throughout. There were no rales or adventitious sounds. The heart borders were within normal limits; there were no murmurs. The abdomen was flat, with no tenderness. The spleen was palpable 3 cm. below the costal margin, but the liver was not palpable. The extremities showed no limitation of motion, but all limbs had a fine tremor on motion. The axillary lymph nodes were not palpable, and the inguinal lymph nodes were not enlarged. The skin was clear, except for a suggestion of pigmentation along the lateral inferior orbital aspects. The reflexes were normal throughout.

Examination of the blood revealed a red-cell count of 4,630,000, with a hemoglobin of 90 per cent, and a white-cell count of 5500. During the next 18 days the red-cell count gradually fell to 2,640,000, the hemoglobin to 52 per cent and the white-cell count to 3750, the differential count showing a marked shift to the left. During the same period the sedimentation rate rose from 8 to 29 mm. per hour. Repeated smears for malarial parasites were negative, as were blood serologic studies. Agglutination tests for the organisms of typhoid, paratyphoid, typhus and undulant fever were negative. Roentgenograms of the chest were normal. Urinalyses were negative. The total blood protein was 8.4 gm. per 100 cc., with 4.8 gm. of albumin and 3.6 gm. of globulin. The thymol-turbidity test was 19 units; the cephalin-flocculation test was ++++, and the icterus index was 8.2. Blood smears and blood cultures (some on N.N.N. mediums) were negative. Marrow smears and cultures were negative for organisms. Gross and microscopic study of the axillary lymph nodes revealed no pathologic changes. Formol-gel tests showed solidification and opacity at the end of 3 hours. Smears from a splenic puncture performed on March 8 revealed typical Leishman-Donovan bodies within endothelial leukocytes. The antimony serum test (performed after the patient had received 0.6 gm. of Neostibosan) was negative.

Although malarial parasites could not be demonstrated, the clinical course resembled that of malaria, and the patient was therefore given a therapeutic trial of quinacrine. The skin became markedly yellow, but there was no improvement. After 10 days of hospitalization the patient was given 240,000 units of penicillin daily for 3 days, but there was no alleviation of symptoms. By that time the spleen was palpated 7 cm. below the costal margin. The liver became palpable, and a small group of lymph nodes in the left axilla became palpable. The patient lost 4 pounds in weight despite a fair appetite and a high-calorie diet. The temperature continued to show a septic rise, varying between 102 and 104°F. Day and night 4-hour temperature readings were started, and it was noted that frequently there was a second elevation during the 24-hour period. A transfusion of 500 cc. of whole blood was given during the last week of February, and another was given during the 1st week in March.

When the diagnosis of visceral leishmaniasis was confirmed by demonstration of the organisms in the splenic pulp, specific antimony therapy was instituted. A total of 4.2 gm. of Neostibosan in fifteen divided doses was given intravenously over a period of 15 days. Within 48 hours the temperature was reduced to nearly normal limits; the appetite improved remarkably, and the profuse perspiration stopped. The spleen in the area of the puncture remained

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§Burchenal, J. H., and Woods, R. P. Visceral leishmaniasis: report of three cases of its occurrence in members of armed forces of United States. *War Med.* 7:173-177, 1945.

tender. During the following 2 days the splenic tenderness increased, with a concomitant increase in the temperature, which at one time reached 102°F. This splenic tenderness was believed to be caused by a small, traumatic, subcapsular hemorrhage. Within 2 days the perisplenitis decreased slowly until the pain entirely disappeared within a month. The spleen decreased slowly in size but remained palpable at the end of 1 month of treatment. The pigmentation around the eyes was no longer detected at that time. On March 27 examination of the blood revealed a red-cell count of 4,160,000, with a hemoglobin of 80 per cent, and a white-cell count of 9000; the sedimentation rate was 20 mm. per hour. The gain in appetite, weight and strength was steady, and the patient was discharged from the hospital on April 13.

A case of visceral leishmaniasis (kala-azar) is reported.

The possibility of visceral leishmaniasis should be considered in patients with fever of undetermined origin, leukopenia and splenomegaly who have resided in an endemic area.

CO-EXISTENT PRIMARY CARCINOMA OF THE FALLOPIAN TUBE AND OF THE BREAST

Report of a Case

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THE purpose of this paper is to discuss primary carcinoma of the fallopian tube, and to submit a report of the first case at the Worcester City Hospital of carcinoma of the fallopian tube and carcinoma of the breast in the same patient. As in the vast majority of cases reported in the literature, the diagnosis of tubal carcinoma was not made preoperatively. It was only suspected during the operation for another pelvic disorder and was confirmed by routine pathological study of the tissues removed during the operation.

Since Rokitansky's original pathological description in 1861 and the first accredited case report presented by Orthmann in 1886, only 449 cases of primary carcinoma of the fallopian tube have been reported in the literature, according to a recent review by Mitchell and Mohler.[1] From figures presented by various clinics these authors estimate that the incidence of the disease among genital-tract tumors is 0.5 per cent, secondary carcinoma of the fallopian tube being about ten times more frequent. The extreme difficulty in diagnosis without pathological studies of the diseased tubes has been discussed by many authors, and it is only with this fact in mind that Martzloff,[2] allowing for unreported as well as unrecognized cases, estimates the upper limit of incidence of primary tubal cancer to be about 0.5 per cent.

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The importance of a serous or serosanguineous discharge from the cervix as a diagnostic aid in this disease has been emphasized by numerous authors.[2,3] Martzloff[2] states that if recent gestation and disease of the vagina and uterine cavity — especially incipient ulcerating cancer complicated by cervical stenosis — can be excluded, a copious, serosanguineous uterine discharge becomes suspiciously pathognomonic and can be ascribed to an extrauterine origin, logically tubal, and a malignant complication. The symptom complex of an otherwise unexplained intermittent, cramplike, abdominal discomfort relieved by the passage of a watery discharge from the vagina, especially when blood tinged, has been considered to be of diagnostic value by several authors, including Martzloff[2] and Mitchell and Mohler.[1] A further adjunct in diagnosis lies in hysterography, whose value and advisability have been debated by different authors.

The treatment of primary tubal carcinoma consists in surgery, with or without postoperative radium or x-ray therapy. Although Martzloff[2] considered bilateral salpingo-oöphorectomy and panhysterectomy the operation of choice and believed that there was no evidence that radium and irradiation were of value, other authors have taken exception to his opinions. Keith[4] proposed the surgical removal of both tubes and ovaries and all pathologic tissue except the uterus, which is left in situ as a receptacle for radium. He believed that good surgery, in addition to the immediate postoperative use of radium implantation and irradiation, would save a larger percentage of patients than either surgery or x-ray therapy alone.

J. H. (W.C.H. 34082), a 50-year-old Negress, was first admitted to the hospital on September 9, 1945, complaining of intermittent pains in the right lower quadrant and of a lump in the left breast. The abdominal pains, which had occurred at occasional intervals for 5 or 6 years, dating back approximately to the time of the menopause, were described as sharp, intermittent and lasting from 2 to 5 minutes and were unassociated with any genitourinary or gastrointestinal complaints or with any change in position or motion. During the 6 weeks before entry these pains had become more frequent, occurring several times a day, occasionally being associated with slight nausea but never with vomiting. The mass in the left breast had first been noted approximately 2 years before entry. It had grown slowly in size and had produced no symptoms. The patient also complained of occasional low-back aches. She denied any weight loss, anorexia or vaginal discharge.

The family history was extremely interesting in that 5 relatives of her father had died of cancer — 1 of carcinoma of the stomach, 2 of carcinoma of the breast and 2 of carcinoma of the rectum.

Physical examination was essentially negative with the exception of the left breast, the abdomen and the pelvis. In the upper and outer quadrant of the left breast there was a palpable, tangerine-sized mass, which was firm, nontender and firmly attached to the adjacent glandular structures and to the overlying skin. There was no bleeding or discharge from the nipple. Palpation of the abdomen revealed a round, firm, nontender grapefruit-sized mass in the left lower quadrant. The right vault was normal, but in the left vault the mass described above could be palpated. On bimanual examination a hard solid mass was palpated in the region of the uterus.

Laboratory examination was essentially negative except for a red-cell count of 3,790,000 and hemoglobin of 68 per cent.

On September 14 the patient was operated on with a preoperative diagnosis of fibroid uterus, left ovarian cyst and carcinoma of the left breast. Palpation of the abdomen disclosed that the large tumor on the left extending upward to the umbilicus had disappeared. The fibroid uterus, however, was still easily palpable. Through the usual subumbilical incision the peritoneum was opened, and a large amount of chocolate-colored fluid escaped. The omentum was observed to be adherent to the peritoneum throughout the lower half of the abdomen. The fluid was syphoned; the uterus was elevated and found to contain numerous subserous fibroids varying in size, the largest being at the fundus. This was used as a tenaculum, and a large ruptured ovarian cyst was delivered by blunt and sharp dissection from the left broad ligament. The left tube presented a large hydrops. Both the broad ligament and tube were double clamped distally, and their proximal ends were clamped and divided, the mass being removed in toto. A supravaginal hysterectomy was then performed in the usual manner. Following the abdominal operation the tumor of the left breast was removed, together with a large portion of breast tissue. The patient had an uneventful course following this operation.

Since microscopical studies of the breast tumor revealed a primary carcinoma, a left radical mastectomy was performed on the 10th postoperative day. Again, the postoperative course was uneventful with the exception of the anemia, which was treated with iron and whole-blood transfusions. The patient was discharged on the 23rd hospital day. After discharge the patient felt well, gradually regained strength and had gained 8 pounds when last seen, 5 months following the first operation.

Gross pathological inspection revealed a funnel-shaped tube measuring 12 by 2.5 by 0.5 cm., with a dull and shaggy serosa. The wall was thick and fibrous, at one point measuring 1.5 cm. in thickness. The specimen showed yellow-gray necrosis resembling caseation. The tumor of the breast measured 12 by 8 by 4 cm., with a deeply pigmented, roughly elliptical piece of skin measuring 3 by 2.5 cm. On section this specimen showed a mottled, dense, yellow-gray surface sharply demarcated from the circumferential tissue. The rest of the breast tissue was abundant, gray and firm.

Microscopic examination of the tube disclosed a solid mass of tumor cells filling the lumen, without any attempt at gland formation. Under high-power inspection these cells had an indistinct cell membrane. The nuclei were mostly oval and vesicular, with rare nucleoli. Many mitoses and a few stroma cells were seen.

The breast showed strands of tumor cells with little stroma. The cells had poorly staining cytoplasm and dark nuclei. Few mitoses were present. In some areas there were wide bands of connective tissue.

The diagnoses were primary carcinoma of the fallopian tube and primary medullary carcinoma of the breast.

From a pathological point of view, attention should be drawn to the difficulty in differentiating tuberculosis and carcinoma of the tube. The former pinches off tiny groups of epithelial cells of the mucosa in such a way that they may present a picture that simulates carcinoma. In all cases of tubal carcinoma a search for the giant cells of tuberculosis is therefore essential.

* * *

A few of the more important considerations regarding the incidence, diagnosis and treatment of primary carcinoma of the fallopian tube are discussed.

A report of the first case of this disease diagnosed in this hospital is presented in which the rare primary tubal carcinoma was associated with a primary carcinoma of the breast in a patient whose family history included 5 cases of deaths due to cancer. Although 30 per cent of cases of primary carcinoma of the fallopian tube are bilateral, inasmuch as the diagnosis was made only by routine pathological examination of tissue removed at operation for a fibroid uterus and ovarian cyst, and also because the case was further complicated by a second major operation, a radical mastectomy, it was not deemed advisable to subject the patient to further surgery. X-ray and radium therapy were not given the patient.

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COMPLETE ABSENCE OF LOCHIA FOLLOWING DELIVERY*

Report of a Case

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THE characteristic bloody discharge that follows childbirth has always been considered such a fundamental phenomenon of parturition that it is designated by the word "lochia," derived from a Greek word meaning "woman in childbed." Complete absence of lochial discharge following the birth of a viable infant has not, to our knowledge, been reported. In 1922 Kickham[1] reported the case of a patient delivered by cesarean section in which there was no grossly demonstrable cervix or cervical opening; there was no sign of vaginal discharge until fifteen hours post partum, when a thin serous fluid, which gradually became blood stained, appeared and continued to be discharged intermittently until the patient left the hospital twenty-two days later. Sperling[2] noted that involution occurred more quickly following cesarean section, and believed this to be due to a diminished wound surface — in cesarean section only the body of the uterus is wounded, whereas in delivery through the pelvis the factors of trauma to the cervix and to the vagina are added. DeLee,[3] commenting on Sperling's article, states, "The small amount of lochia after cesarean section is remarkable; indeed, one often suspects lochiostasis, and attempts unnecessary drainage." Bardenhauer, who is quoted by Sperling as making the same observation, considered the paucity of lochia to be due

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to acidosis and mentioned an attempt to control the amount of lochia by diet.

In the following case, in which the patient was delivered by cesarean section at thirty-six weeks because of toxemia, a contracted pelvis, elderly primiparity and a breech presentation, there was no vaginal discharge during the twenty-one days of an otherwise normal postoperative and puerperal course. During that time the temperature rose above normal on three scattered occasions, but never above 99.4°F.

Mrs. C., a 40-year-old primigravida, was first seen during the 12th week of pregnancy. There had been no serious illnesses and no operations. The periods, which had begun at the age of 12 years, occurred regularly every 28 days, but the flow for the preceding 10 years had been scanty and of only 2 days' duration. The last regular period had begun on July 24, 1944. Physical examination revealed no abnormalities. The blood pressure was 138/86, and urinalysis was negative.

The pregnancy continued uneventfully until the 34th week of gestation, when there was an elevation of blood pressure to 142/110; urinalysis revealed the smallest possible trace of albumin, and there was slight edema of the hands and ankles. The patient was treated at home for a week with bed rest, mild sedation, a salt-free diet and saline catharsis. This treatment brought no improvement, and the patient was admitted to the Cardinal O'Connell House, St. Elizabeth's Hospital. The blood pressure was then 150/114. The urine showed a trace of albumin, and the edema had increased. After a week of complete bed rest, sedation, saline purgation and intravenous hypertonic dehydration, the blood pressure had risen to 178/114. The patient became irritable and apprehensive, and there was upper abdominal distress and headache. She was then 36 weeks pregnant. The fundus was palpated 3 fingerbreadths below the ensiform. The fetus was in the left sacroanterior position, with the breech in the false pelvis. The pelvic outlet was narrow, and the cervix long and firm.

On March 31, 1945, after a transverse cervical cesarean section under spinal anesthesia, a female infant weighing 4 pounds, 14 ounces was delivered. The infant was otherwise normal in all respects and was discharged from the hospital in 35 days, weighing 5 pounds, 9 ounces. The infant was not breast fed. One ampule of ergot was administered intramuscularly following delivery. The intravenous route was not used because of the mother's hypertension. The placenta and membranes were expressed intact after they had begun to separate.

On the following day the blood pressure had dropped to 114/96. The temperature was 99.4°F., the pulse 84, and the respirations 20. There was no nausea or vomiting. The edema had disappeared; the patient felt well and was excreting a normal amount of urine. Since returning from the operating room there had been absolutely no lochial discharge. The fundus was nontender and firm, and could be felt 1 fingerbreadth below the umbilicus. The temperature on the 1st, 4th and 10th post-partum days was slightly elevated; the highest reading was 99.4°F. The postoperative course was otherwise entirely uneventful. The patient was allowed out of bed on the 7th postoperative day.

There was no distention and no elevation of pulse or respirations. The vulval pads were carefully inspected and remained perfectly dry until discharge from the hospital. The fundus, which was felt each day, continued to be nontender, and involution progressed normally, so that the fundus was felt 3 fingerbreadths above the symphysis on the 12th post-partum day. The patient was discharged on the following day, when the blood pressure was 120/90 diastolic.

On the 21st day following delivery, menstrual flow began. The amount of flow was slightly more profuse and lasted 1 day longer than the usual period. The flowing was painless, and there were no clots. On examination, 4 weeks after delivery, the fundus was in anterior position, and was ½ larger than normal. There was no vaginal discharge, and the general condition was excellent. Two weeks later the uterus was normal in size and position. There was no discharge, and the urine was normal. The blood pressure was 124/84. Fifteen weeks after delivery, the blood pressure was 128/78, urinalysis was negative, the fundus was normal in size and position, and the patient felt well. The periods, which were scanty and of 2 days' duration, had occurred regularly at 28-day intervals.

Involution, the change in the size of the uterus following delivery, is one of the most striking examples of atrophy known. The average post-partum uterus is said to weigh in the vicinity of 2½ pounds, or 1000 gm.,[4] half as much a week later, from 350 to 375 gm. at two weeks and 50 gm. when normally involuted at six or seven weeks. The structures involved in this process are the muscle fibers, the blood vessels and the decidua, especially at the placental site. The amount of lochia has been variously estimated as between 500 and 1000 cc.,[5] although we have found no record of accurate measurement; during the first three days it is said to be profuse enough to soak a perineal pad in six to eight hours.[6] The bloody discharge is generally believed to last from ten days to two weeks.

Knowledge concerning the processes of regeneration of the uterine mucosa following labor may be said to have begun with the monograph of Friedlander,[7] written in 1870, although William Hunter,[8] a century earlier, had stated that "the decidua is an efflorescence of the inner coat of the uterus, and is therefore shed as often as the woman bears a child or suffers a miscarriage." In 1931 Williams[9] described in detail the regeneration of the uterine mucosa following delivery; he stated that the cervical mucosa is not cast off and is completely restored by the end of the first week post partum, although the tissue beneath it may long remain infiltrated with blood; he also observed that, at the end of fourteen days, the uterine cavity is completely covered by endometrium and that by the third week the uterine mucosa is entirely restored, with the exception of the placental site, which disappears in about seven weeks. These changes are brought about by encapsulation, by orderly invasion and, finally, by exfoliation by sensible and insensible lochial discharge and fibrolysis. Since the noticeable lochial discharge continues for about two weeks and the regeneration of the placental site is not complete for seven weeks (and only then by a process of exfoliation), it is evident that this material must disappear by some lytic action that causes either its absorption or its insensible discharge. To explain this part of the regeneration Jochman[10] postulated the presence of a proteolytic enzyme in the lochia, and both Irving[11] and Beck[12] mentioned a breakdown of protoplasm during the puerperium into simpler substances that are eventually excreted by the kidneys, as evidenced by the fact that nitrogen elimination is doubled during that time.

A possible explanation of the case reported above is that the patient was an elderly primigravida whose past history of short, scanty periods indicated a thin endometrium. It has been shown by Rock[13] that in

these cases the predecidua — and, it is assumed, in pregnancy the decidua as well — is less thick than that usually found, although the cytology denotes the estrogen-progesterone relations to be normal. In other words, there is simply a paucity of normal tissue and no interference with fertility. It is possible that the predecidua and decidua in the case presented were of this type. The amazing rapidity with which the endometrial epithelium covers the denuded menstrual surface of the uterus is known, and the process is believed to start before the patient has stopped flowing. In 1901 Krönig[14] pointed out that, although separation of the placenta and membranes usually occurs in the spongy layer of the decidua, it does not occur as schematically as described in the literature, and he showed that the amount of tissue retained varies greatly, consisting in some places of only a few layers of cells and in others of portions of spongy layer measuring several millimeters in thickness. In 1917, after studying 50 cases in which the uterus had been removed at cesarean section, Williams[9] concluded that whereas separation generally occurs in the spongy layer, the line of cleavage is extremely irregular, so that in some places a thick layer of decidua and in others only a few layers of cells remain and that in still others the muscularis is practically bare.

In the case presented above it is possible that, at the time the placenta and membranes were expressed after they had begun to separate, there was little decidua left and that what remained was disposed of by rapid autolysis accompanied by a speedy regeneration of the mucosa. After twenty-one days there was probably some bleeding from the placental site in the process of exfoliation, as noted in 60 per cent of cases by DeLee,[15] with a subsequent resumption of normal menstrual cycles.

* * *

The case of a forty-year-old primigravida delivered by cesarean section four weeks before term is presented. There was complete absence of lochia throughout the puerperium. In other respects, the post-partum course was quite uneventful, and the uterus involuted normally.

A possible explanation for the absence of the lochial discharge is discussed.

The data presented indicate that complete absence of the lochia is compatible with a normal puerperium. Dilation of the cervix or other operative intervention is contraindicated unless symptoms clearly indicate their necessity.

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MEDICAL PROGRESS

THE PHYSIOLOGIC AND CLINICAL SIGNIFICANCE OF PLASMA PROTEINS AND PROTEIN METABOLITES (Concluded)*

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CIRCULATING PROTEIN METABOLITES

The circulating plasma proteins represent one phase in the dynamic equilibrium existing between plasma and tissue proteins. Another clinically important phase of protein metabolism in health and disease is associated with the circulating protein catabolites. These nonprotein nitrogenous substances are the resultants of intermediary metabolism of ingested and tissue proteins. The nonprotein nitrogen of the blood — that portion not precipitated by the usual protein precipitants — is a heterogenous mixture of urea, uric acid, amino acids, creatine, creatinine and a fraction designated as "undetermined nitrogen" that appears to contain polypeptides, various amino acids, adenylic-nucleotide and other components.[103] The relative concentration ranges of these substances are indicated in Table 7.

Most of the end products of nitrogen metabolism are removed in the urine. An inadequate rate of excretion, whether the result of decreased blood flow or of reduction in the proportion of protein metabolites removed, is manifested as reduced clearance of these substances from the blood. The ultimate clinical equivalent is retention of nonprotein nitrogen constituents. The significance of these substances in blood rather than in urine is briefly discussed below.

TABLE 7. *Relative Concentration Ranges of Blood Nonprotein Nitrogenous Constituents.**

CONSTITUENT	PLASMA	BLOOD CORPUSCLES	WHOLE BLOOD
	mg./100 cc.	*mg./100 cc.*	*mg./100 cc.*
Urea nitrogen	13–23[116]	12–22[116]	5–23[117]
Amino acid nitrogen	3.5–6[118, 119]	8.9–13[121]	5–8[103]
	2.9–4.6[120]		
Creatine	0.1–0.5[122, 123]	4–8[116]	4–9
Creatinine	1–1.7[122, 123]	1–3[116]	1–2[103]
Uric acid nitrogen	2–6[124]	1–4[116]	2–4[20]
Ammonia nitrogen	—	—	0.1–0.3[103]
Undetermined nitrogen	2[116]	19[116]	5–19[103]
Total nonprotein nitrogen	20–36[116]	39–61[116]	25–40[103]

*Relative ranges are somewhat modified by the method of chemical analysis, metabolic state and preceding dietary pattern of the subject. In some cases the age, sex and physiologic state influence the normal ranges (amino acid nitrogen, creatine, creatinine and uric acid nitrogen).

Changes in blood nonprotein nitrogen may reflect altered concentration of any of its constituents. Most frequently, marked changes are the result of alterations in urea or undetermined nitrogen, or both. Creatine, creatinine, uric acid and amino acid nitrogen concentrations in the blood are relatively small. Fluctuations are usually not attended by marked changes in the nonprotein nitrogen. Increased nitrogen retention, or azotemia, is the resultant of the rate of nitrogen catabolism, hydration, urine volume, nitrogen excretion and mineral metabolism. Azotemia, therefore, is not in itself necessarily indicative of renal damage or permanently impaired renal function. Several conditions that may be associated with altered concentrations of blood nonprotein nitrogenous constituents are listed in Table 8, and detailed discussions of this subject are available in several texts.[20, 103]

Urea is the chief nitrogenous end product of protein metabolism in mammals. Urea so formed does not enter into further metabolic reactions.[5] The experiments of Bollman, Mann and Magath[125] with hepatectomized dogs demonstrated that the liver was the principal site of urea formation. The bulk of the nitrogen for urea synthesis is derived from the amino nitrogen of the amino acids. Nitrogen from other sources — such as ammonia, absorbed deamination products, amide and other groupings — may be converted into urea. Urea synthesis involves the cyclical participation of several amino acids (arginine, citrulline, ornithine and glutamine), enzymes (arginase), ammonia, carbon dioxide and bicarbonate.[126–128] Interrelations between arginine and ornithine in the process of urea formation have been confirmed by isotopic analysis,[5] but do not completely explain the process of urea formation.[129] Complete details concerning this fundamental process are as yet unknown.

Urea nitrogen comprises approximately 80 per cent of excreted urinary nitrogen. Urea is a readily diffusible nonelectrolyte and appears in relatively equal proportions throughout the body fluids and tissues.[103] Clearance of urea from the blood more accurately depicts renal function than blood urea nitrogen concentration. An increase in the urea nitrogen-nonprotein nitrogen ratio may provide a fair indication of decreased urea clearance.[130] Increased blood urea nitrogen may be the primary result of altered renal structure and function — as

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TABLE 8. *Conditions* Associated with Altered Concentrations of Blood Nonprotein Nitrogenous Constituents.†*

BLOOD UREA NITROGEN	AMINO ACID NITROGEN	URIC ACID NITROGEN	CREATINE	CREATININE
INCREASED CONCENTRATION	INCREASED CONCENTRATION	INCREASED CONCENTRATION	INCREASED CONCENTRATION	INCREASED CONCENTRATION
Decreased renal urea excretion: Glomerulonephritis Congenital renal abnormalities: Hypogenesis Hypoplasia Polycystic disease Local destruction or inflammation: Pyelonephritis Pyonephrosis Nephrosclerosis Cancer Tuberculosis Urinary obstruction Tubule edema: Serum disease Mercury poisoning Tubule obstruction: Sulfonamide crystals Urates Hemoglobin Bence-Jones protein Amyloid deposits Cylindruria Ureteral or urethral lithiasis Prostatic hypertrophy Carcinoma Decreased urine volume (prerenal deviation of water): Shock and hemoconcentration Burns Upper gastrointestinal obstruction Pancreatic fistula Peritonitis Constrictive pericarditis Congestive failure, with decreased renal blood flow Addison's disease Prolonged vomiting Prolonged diarrhea Dehydration Acidosis Excessive protein catabolism: Severe toxic and febrile diseases (infections) Severe thyrotoxicosis Starvation Marked protein deficiency Miscellaneous factors: Hepatorenal syndrome Diabetic acidosis Gout Severe hyperparathyroidism Upper gastrointestinal hemorrhage: Ulcer Varices Cancer Infectious diseases, typhus, pneumonia and so forth Eclampsia	Decreased deamination: Acute hepatic insufficiency: Acute yellow atrophy Toxic necrosis Hepatic carcinoma Thermal burns Increased availability or catabolism: Intravenous amino acid infusion (transient) Hormone administration (variable): Anterior pituitary Thyroxine Adrenocorticosterone Testosterone Leukemia Polycythemia vera Decreased renal function: Hepatorenal syndrome Eclampsia Hemorrhagic shock (?) Ablation of renal function	Abnormal purine metabolism: Gout Increased nucleoprotein metabolism: Leukemia Multiple myeloma Polycythemia vera Pernicious anemia (in remission) Renal abnormalities: Nephritis Nephrosclerosis Essential hypertension Lead poisoning Eclampsia Miscellaneous: Cardiac decompensation Pneumonia Acute hepatic necrosis Osteoarthritis	Increased catabolism: Hyperthyroidism Progressive muscular dystrophy Muscular atrophy Hormone administration (methyl testosterone) Starvation Increased synthesis: High-protein diet Miscellaneous: Intravenous amino acid infusion (if serum creatine previously elevated)	Renal insufficiency: Nephritis Urologic obstruction (rare)
DECREASED CONCENTRATION	DECREASED CONCENTRATION	DECREASED CONCENTRATION	DECREASED CONCENTRATION	DECREASED CONCENTRATION
Decreased urea synthesis: Acute hepatic insufficiency: Acute yellow atrophy Toxic necrosis: Phosphorus, carbon tetrachloride, arsphenamine and cinchophen poisoning Extensive hepatic degeneration: Cirrhosis Cancer Normal pregnancy	Increased demand: Pneumococcal pneumonia Nephrosis (in children) Hormone administration: Insulin Adrenalin	Decreased concentrations not clinically significant	Decreased concentrations not clinically significant	Decreased concentration not clinically significant

*Tabulated by supplementation of original compilation of Peters and Van Slyke.[103] Physiologic variations not tabulated.

†Variations in total nonprotein nitrogen of blood not tabulated. Such variation is the summation of contributing variables. Most frequently, increased nonprotein nitrogen reflects increased blood urea nitrogen and undetermined nitrogen. It is apparent that in some cases other constituents may be involved. Variations of undetermined nitrogen are not tabulated.

in the nephritides — or may occur in the presence of essentially normal renal structure with either normal or temporarily abnormal function ("prerenal azotemia") — as in gastrointestinal hemorrhage or typhus fever. Pathologic variations occurring in several diseases are indicated in Table 8.

Protein metabolism is essentially the metabolism of the amino acids.[103] Amino acids absorbed from the intestine — neither deaminated nor synthesized into protein by the liver and supplemented by similar fractions derived from the constant interchange of dietary and tissue protein — constitute the circulating amino acid nitrogen of blood. The amino acid nitrogen concentration of plasma remains quite constant at a level approximating 3 to 6 mg. per 100 cc.[119] Transient physiologic increases occur following ingestion of a protein meal or parenteral amino acid administration. The liver is the primary site of the deamination of amino acids, and approximately 90 per cent of its functional capacity must be interfered with before deamination is impeded. When urea forming or deaminizing functions of the liver are impaired, the blood amino acid nitrogen increases and the blood urea nitrogen decreases. Urinary amino acid excretion correspondingly increases. With extensive hepatic damage, leucine and tyrosine crystals may be identified in the urine.[103, 131] Specific amino acid excretion in the urine may occur with rare congenital defects in amino acid metabolism. A partial list of diseases associated with pathologic alterations in amino acid nitrogen is indicated in Table 8. Parenteral administration of amino acid hydrolysates induces a moderate transient increase in blood amino acid and urea nitrogen. Patients with previously elevated serum creatines and associated alterations in utilization or disposal of creatine may evidence a further increase in serum creatine following amino acid administration. The increased creatine is probably derived from the methionine and arginine of the hydrolysate.[132] Decreases in serum inorganic phosphate attendant to parenteral amino acid administration have been observed.[133] A rapid increase of amino acid nitrogen to levels greater than 10 mg. per 100 cc. on infusion of an amino acid digest may be associated with nausea and vomiting. Glutamic or aspartic acids may be responsible for this phenomenon.[133] An increase in plasma amino acid nitrogen (in rats) associated with peripheral circulatory failure and hemorrhagic shock presumably affords an unfavorable prognostic sign.[134] Elevation of the plasma alpha amino nitrogen levels has been observed in thermal burns.[135]

Creatinine, another component of the nonprotein nitrogen of the blood, is the anhydride of creatine. The formation of creatinine from creatine may proceed without intermediate steps[136] or may be related to phosphocreatine.[137] Isotopic technics have indicated that creatine formation is dependent on the formation and methylation of glycocyamine. Choline or methionine constitutes the principal source of methyl groups.[138] The nitrogenous constituents of creatine appear to be derived from glycine and arginine.[5] It is thus apparent that the metabolism of creatine is closely related to choline and at least two amino acids — methionine and arginine. Blood creatine concentration in health is usually constant and clinically insignificant. It may be increased in hyperthyroidism,[123] various severe or terminal illnesses and, if initially elevated, following infusion of an enzymatic hydrolysate of casein.[132] Blood creatinine concentration may vary considerably in disease. Increased concentration may occur in any disease in which marked nonprotein nitrogen retention occurs. Markedly increased blood creatine and creatinine are probably the result of increased endogenous protein catabolism in addition to some degree of impaired excretion. Variation in the rate of excretion of creatine or of creatinine may result from changes in the rate of synthesis of creatine from its precursors, in the ability of tissues to store or to liberate creatine or in the rate or direction of creatine-phosphocreatine reactions.[139]

Uric acid, in man, is the chief end product of exogenous and endogenous nucleoprotein metabolism. In both its synthesis and its excretion, uric acid is closely associated with the amino acids. Glycine, alanine, aspartic, glutamic and pyruvic acids increase uric acid excretion; benzoic and phenylacetic acids depress its excretion. Details of uric acid metabolism remain obscure.[140] The normal concentration of blood uric acid (2 to 6 mg. per 100 cc.) is little affected by purine-rich foods and is not directly related to the level of nonprotein nitrogen or urea. Abnormal increases of blood uric acid may occur in association with decreased urate elimination by the kidney, primary alterations in nucleoprotein metabolism such as gout, increased endogenous nucleoprotein catabolism as in leukemia or pernicious anemia or excessive nucleoprotein or purine supply associated with these metabolic defects. Destruction of uric acid does not appear to take place in human beings. Like other nonprotein nitrogen catabolites, uric acid is excreted preponderantly in the urine. Urates are freely diffusible, are equally distributed in plasma and glomerular urine and are limitedly concentrated by the tubules. The low tubular concentrating power accounts for the relatively high blood uric acid concentration.[141] Uric acid excretion is related to urinary volume and may be increased by the diuresis attendant to continuous infusion of glucose with maintained hyperglycemia.[142] Functional inhibition of urate excretion may explain hyperuricemia. The etiology of tissue urate deposits remains unknown. Hyperuricemia, local trauma, infectious agents, circulatory impairment and primary local tissue changes favor urate precipitation.[141] Uricemia associated with several pathologic states is indicated in Table 8.

Ammonia, another of the nitrogenous end products of protein metabolism, results from kidney deamination of alpha-amino groups of amino acids. Dietary ammonia derived from protein digestion products is not a source, and urea is not an intermediate in ammonia formation.[5] Since the ammonia nitrogen concentration of blood is quite small (less than 0.3 mg. per 100 cc.) and since conditions that produce a marked increase in urinary ammonia excretion do not appreciably alter blood concentrations,[103] blood or plasma ammonia nitrogen appears to be of little clinical importance. Urinary ammonia excretion, on the other hand, is of considerable clinical significance, since it represents an attempt to conserve body base.[143]

Undetermined, or residual, nitrogen comprises the final group of nonprotein nitrogenous substances resulting from protein metabolism. Undetermined nitrogen, apparently a cellular component, is said to be composed of hippuric acid, nucleotides and histones.[20] Its clinical and metabolic significance is not clear, although a rather large European literature has accumulated. Undetermined nitrogen is usually elevated in disturbances that cause nitrogen retention. In some cases undetermined nitrogen — for practical purposes the difference between urea nitrogen, creatinine nitrogen and the total nonprotein nitrogen — may be of clinical significance. For example, hemorrhage into the gastrointestinal tract is associated with azotemia, which appears to be largely the result of absorption of nitrogenous components from the enteral blood.[144, 145] Impaired renal function may also be a factor.[146] Continued elevation of the blood urea nitrogen may have prognostic significance.[145] Proportional increases in the undetermined nitrogen fraction may be as great as or greater than increases in urea nitrogen per se and may afford a means of detecting continued gastrointestinal hemorrhage. The azotemia of intestinal obstruction is said to be more closely related to undetermined nitrogen than to urea.[147] In some cases of eclampsia or chronic nephritis with nitrogen retention, undetermined nitrogen may represent the greatest proportional increase in nonprotein nitrogenous substances.[20]

Amino Acid and Nitrogen Metabolism

The anabolic phase of protein metabolism, that of protein synthesis, was long considered a relatively static process largely restricted in the adult to replacement of the endogenous protein loss of "wear and tear." It was believed by some that body protein was composed of two distinct categories: fundamental structural tissue protein and the more readily utilizable deposit protein of cells and extracellular fluid. It was thought that tissue protein, once formed, remained relatively unchanged until destroyed by metabolic wear and tear. Acute negative nitrogen balance and hypoproteinemia were considered manifestations of deposit protein withdrawal. The current concept of protein metabolism was evolved from two sources: the suggestion that intracellular protein undergoes continuous change during nitrogen equilibrium at a rate commensurate with nitrogen intake and utilization[148]; and observations on plasma protein regeneration and nitrogen balance in the bled, protein-depleted dog subsequent to protein feeding.[1] This theory postulates a continuous dynamic exchange of tissue and plasma proteins.[1, 2] Direct verification and extension of this concept at the fundamental level of molecular regeneration, involving the constant transfer of specific chemical groups, was obtained by using specific amino acids labeled with isotopes.[5] Nitrogen in several amino acids was replaced by a heavy atomic analog or isotope, and in some cases, hydrogen of the amino acid carbon chain was also replaced by its heavy isotope, deuterium. By tracing the course of these tagged groups throughout the body, it became evident that both amino nitrogen and the remainder of the amino acid were incorporated in many tissue proteins of the body, including those of the plasma and erythrocyte. It was demonstrated that transfer of entire chemical groups between the various fed and in situ tissue amino acids, as well as their metabolites, constantly occurred. It was inferred that the peptide bonds, which are the chief links binding amino acids into protein structures, are not fixed but rather are rapidly exchanging one constituent group for another. These demonstrated metabolic exchanges, involving both degradation and synthesis, imply enzymatic reactions. Such reactions are not isolated events. Each requires the simultaneous occurrence of others — for example, creatine formation involves groups derived from at least three different amino acids. Two of these amino acids promptly replace their lost fragments from others; other reactions involve cycles, such as urea formation. These metabolic exchanges constitute a fundamental part of the biologic process.[5]

Development of the concept of dynamic equilibrium between tissue and plasma proteins has been attended by observations pertaining to other fundamental roles of certain amino acids in metabolism. The early experimental observations of Osborne and Mendel[149] provided evidence that two amino acids (lysine and tryptophane) were essential for growth of the rat. This work was extended by the use of diets containing some twenty purified amino acids. When appropriate mixtures were fed to young rats, growth was maintained; in older rats, weight and health were maintained. Omission of individual amino acids indicated that some were indispensable for growth and maintenance and that others were not. By these criteria, a group of ten amino acids were found to be essential for growth of the rat.[3] Nitrogen balance studies, utilizing synthetic diets, were extended to adult man and culminated in the observations that only eight amino acids were essential for maintenance of nitrogen

equilibrium during the periods of observation[3, 4] (Table 9).

Nitrogen balance describes the relation between nitrogen intake and output. Positive balance means that less nitrogen is lost from the body than is taken in — nitrogen is being stored. Negative nitrogen balance is exactly the opposite. A positive nitrogen balance represents a desirable state of retention and utilization of protein. The metabolism of amino

TABLE 9. *Indispensable or Essential Amino Acids.**

IN RATS	IN MAN
Leucine	Leucine
Isoleucine	Isoleucine
Valine	Valine
Lysine	Lysine
Arginine†	—
Histidine	—
Threonine	Threonine
Tryptophane	Tryptophane
Phenylalanine	Phenylalanine
Methionine	Methionine

*Classification of the usual 22 amino acids as essential or nonessential has resulted largely from the work of Rose[3] and his colleagues. In rats an essential amino acid is defined as "one which cannot be synthesized by the animal organism, out of the materials ordinarily available, at a speed commensurate with the demands for normal growth."

In man nitrogen-balance studies in young adults have been the principal technic used to examine the essentiality of amino acids.[4]

†Arginine can be slowly synthesized by the rat, but not at a sufficiently rapid rate to maintain reasonably good growth.

acids and proteins is partially reflected in the nitrogen balance of the individual. Normal growth[150] and maintenance[151] are associated with positive nitrogen balances. Various pathologic states are associated with a loss of nitrogen in their acute or chronic phases, or both.[152, 153] The negative nitrogen balances observed in these conditions are rather difficult to explain. Apparently, negative balance is not the direct result of diminished protein absorption, disuse atrophy, local toxic tissue destruction, accelerated energy expenditure or heat production or the degree of febrile reaction. Protein metabolic pathways may be distorted, and protein synthesis diminished. The duration and degree of retarded protein synthesis presumably varies inversely with the previous nutritional state and directly with the severity of the disease or injury. It may represent a reparative rather than a primarily destructive process.[153] Nitrogen lost in such conditions is thought to be derived primarily from tissue protein. This nitrogen loss may be influenced by endocrinologic interrelations. The effect of anterior pituitary growth hormone on nitrogen metabolism in the growing child is well known. Androgens, such as testosterone propionate, initiate nitrogen retention in normal men and women,[154] as well as in eunuchoidal males,[155] and have been observed to induce nitrogen retention in a female patient with Cushing's syndrome.[156] Such hormone administration appears to exert a somatotropic effect on protein deposition, being associated with decreased urinary excretion of phosphorus, potassium and creatine. Despite quantitative nitrogen retention associated with the administration of chorionic gonadotropin, testosterone propionate or methyl testosterone, these hormones apparently exert little effect on either the total circulating plasma protein or the concentration of albumin or globulin.[157] Relative hypoproteinemia occurring shortly after androgen administration suggests either accelerated formation of tissue protein derived from plasma protein or preferential synthesis of the tissue protein.[158]

The relation of adrenal steroids to nitrogen metabolism is not clear. In general, the metabolic effect attending administration of that group of adrenocortical steroids having an oxygen in the C-11 position may eventuate in negative nitrogen balance. It has been suggested that the negative balance represents heightened gluconeogenesis, a manifestation of increased protein catabolism,[159] or conversely, lowered protein synthesis, a manifestation of decreased protein anabolism.[160] It has also been suggested that adrenocortical hormone directly influences the conversion of tissue proteins to amino acids[161] and enhances the rate of amino acid deamination[162] and that the adrenal cortex elaborates a nitrogen-sparing factor. Impaired production of this factor may be responsible for the protracted biologic and metabolic abnormality following acute injury,[160] characterized as the so-called "alarm reaction" of Selye.[163] The negative nitrogen balance associated with impaired synthesis or protein depletion, or both, may eventually condition the occurrence of a clinical protein-deficiency state. Provision of a high protein intake during both the immediate catabolic and later convalescent phase following infection or injury minimizes this conditioned malnutrition.

The amino acids are usually obtained from dietary sources. Peptic, tryptic and enteric digestion of protein provides assimilable amino acids that are largely absorbed unchanged in the small intestine but may enter the circulation via thoracic-duct lymph. Absorbed amino acids are readily taken up by the tissues, particularly the liver.[164] Some amino acids serve as precursors or constituents of biologic substances, such as vitamins, co-enzymes, hormones and various detoxication products. Some are converted into tissue proteins. Others may be utilized for energy or contribute directly to the various nonprotein nitrogen moieties. Some of the metabolic implications of the essential amino acids are given in Table 10.

The metabolism of the amino acids involves deamination (removal of the alpha-amino group), amination (the reverse of this procedure) and transamination (amination without participation of ammonia).[176] The energy derived from these metabolic reactions is reported to account for the elevated basal metabolic rate, or the so-called "specific dynamic action," following ingestion or infusion of proteins or amino acids.[177]

The continuous formation of plasma proteins is dependent on the supply and adequacy of amino acids and the integrity of their synthesis. Information pertaining to the amino acid composition of and that associated with antibody formation and immune response may involve different amino acids in varying degrees. On the other hand, amino acid contributions derived from injection of whole blood,

TABLE 10. *Metabolic Implications of the Essential Amino Acids.*

AMINO ACID	GENERAL CLASSIFICATION	HUMAN PLASMA COMPOSITION*		KNOWN METABOLIC FUNCTIONS†	CLINICAL SIGNIFICANCE‡
		ALBUMIN %	GLOBULIN %		
Leucine	Mono-amino	11.9	8.9–9.3	May contribute to acetone-body formation in rat[165] by conversion to trihydroxybutyric acid; carbon chain indispensable.	Presumably ketogenic
Isoleucine		2.0[165]	?	May contribute to either acetone-body formation or glycogen deposition under appropriate conditions[166]	Possible limiting factor in human albumin[167] and plasma therapy
Valine		4.1[168]	?	Glycogenic; decreases experimental ketosis in rats.	Deprivation in rats leads to hyperesthesia and severe unco-ordination[169]
Lysine	Di-basic	5.8	6.7	Unlike other amino acids does not readily undergo reamination; therefore, presumably represents isolated example of amino acid not reversibly involved in the nitrogen shift; unlike other essential amino acids cannot be replaced by any of its deamination products in metabolism.[5]	Forms cadaverine, a ptomaine, on decarboxylation; this is probably of little clinical significance.[170]
Arginine		6.15	4.8–5.6	Forms ornithine and urea — both concerned in mechanism of urea formation[126]; one of precursors of creatine[136] and probably glutamic acid.	Deficiency may impede spermatogenesis[171]
Histidine		3.5	2.5	Splitting of carbon chain, catalyzed by enzymes, may yield glutamic acid or histamine, or both.	Constituent of normal pregnancy urine, but not pathognomonic of pregnancy; its elaboration not essential for maintenance of positive nitrogen balance in man (hence dispensable).
Threonine	Hydroxy	5.03	7.3–8.3	May be glycogenic; appears to decrease experimental ketonuria in rat.	
Tryptophane	Aromatic heterocyclic	0.19	2.1–2.9	Metabolic precursor of kynurenic acid and indican, which may be normal urinary constituents, and possibly one of precursors of urinary pigment, urochrome; intestinal bacterial flora produce indole and skatole from this amino acid.	Odor of feces; deficiency leads to cataract formation in the rat[172]; human albumin deficient in tryptophane.[167]
Phenylalanine	Aromatic	7.8[168]	5.9[168]	May be converted to tyrosine or pursue another metabolic path to phenylpyruvic acid; when converted to tyrosine becomes implicated in synthesis of melanin (skin pigment), thyroxine (diiodotyrosine) and adrenaline; defect in conversion of phenylalanine to tyrosine may be associated with ascorbic acid metabolism (vitamin C),[173] particularly in premature infants.	Albinism may result from enzymic failure of melanin production; alcaptonuria results from incomplete metabolism of phenylalanine and tyrosine and is result of homogentesic acid excretion in urine; oligophrenic phenylpyruvica probably represents failure of conversion of phenylalanine to tyrosine,[174] and is associated with mental deficiency and neurologic stigmas.
Methionine	Sulfur-containing	1.28	1.1–1.5	Methionine sulfur may be converted to cystine sulfur[5]; by relation to cystine, may be implicated in glutathione formation, which is important respiratory enzyme; may be precursor of taurine, bile component; by contributing methyl groups, is associated with in vivo synthesis of choline and creatine[5]; if converted to cystine, or by contributing methyl groups, may be involved in certain detoxication phenomena.	Insulin contains cystine; methyl group deficiency may result in fatty livers and abnormal creatine metabolism; deficiency is associated with susceptibility of rat to virus of infectious hepatitis[175]; bromobenzene detoxification; cystinuria is congenital defect of cystine metabolism; is involved in conjugation of benzoic to hippuric acid.

*Data pertaining to the amino acid composition of protein is limited by the inadequacy of present analytic methods. The major part of the plasma protein composition data is derived from Brand, Kassel, and Saidel.[82] The figures for globulin represent values determined for purified gamma globulin and fraction III-2 (beta) globulin.

†All amino acids undergo deamination yielding amino and other groups to the body metabolic pool.

‡Specific clinical significance, except that pertaining to maintenance of nitrogen balance and certain congenital defects, is not well known at present.

plasma protein, therefore, has clinical importance. The protein depletion and requirement attendant to burns, that occurring in response to various diseases, such as malnutrition, nephrosis or hepatitis, plasma or plasma fractions may vary. The partial amino acid composition of the major plasma protein components has been tentatively stated.[82] Albumin contains at least five and probably six essential

amino acids — lysine, methionine, tryptophane, threonine and leucine and probably arginine — but is relatively low in tryptophane and isoleucine.[167, 178] Gamma globulin similarly contains at least these five essential amino acids with relatively large numbers of hydroxy-amino groups affording easily labile hydrogen bonds; beta globulin and fibrinogen include at least four of the essential amino acids, apparently lacking lysine.

Many amino acids are intimately concerned with the metabolism of carbohydrate. There is some evidence that much of the carbohydrate formed after the administration of glycogenic amino acids such as glycine does not originate by direct conversion of the amino acid[179] but may depend on enzymatic conversion of some intermediary metabolite.[176] Many of the vitamin B components involved in carbohydrate metabolism function as prosthetic groups of enzymes. Undoubtedly, specific amino acid complexes are necessary for the formation of the appropriate enzyme system.

The relation of specific amino acids to some mechanisms of immunity is of considerable interest. It is thought that simple amino acids, as such, are not of primary significance in this regard. They are, however, indirectly involved as structural units in more complex proteins. According to Pauling's[180] theory of antibody formation, reactive antigen having a specific pattern penetrates to the sites of globulin formation and stimulates synthesis of specifically modified antibody globulin. The antibody globulin chain is modified, during synthesis, by coiling about the reactive antigen groups in such fashion as to template their configuration by surface approximation — thus achieving specificity.[180] The spatial modification of the newly synthesized antibody globulin may owe its lability to the large number of easily converted hydrogen bonds contributed by hydroxy-amino acids, such as tyrosine, serine and threonine.[181] Threonine is an indispensable amino acid and must be supplied preformed in the diet. Tyrosine may be derived from phenylalanine, another essential amino acid. These amino acids are components of gamma globulin. Analyses of large quantities of several specific antigen-antibody precipitates have indicated an amino acid composition similar to that of typical serum globulin.[182] Application of isotopic analytic methods has demonstrated that protein antibody in actively immunized animals takes up dietary nitrogen in a manner similar to that of plasma globulin and other tissue proteins.[6, 7] The available evidence, therefore, indicates that specific protein antibody synthesis is merely one phase of general protein synthesis and is at least partially dependent on adequate amino acid supply and metabolism.

Summary

The application of newer experimental technics to problems of protein structure and function has abetted clinical understanding of plasma protein significance. This paper attempts to correlate some of the recent data derived from physiologic, biochemical, physicochemical, nutritional, immunologic and clinical investigations in terms of their clinical implications.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 33021

PRESENTATION OF CASE

A twenty-seven-year-old, single, unemployed man entered the hospital because of chronic diarrhea and weight loss.

Five years before admission the patient had suddenly developed lower abdominal cramps and profuse watery diarrhea. He was admitted to a hospital, where a diagnosis of chronic ulcerative colitis was confirmed by x-ray and sigmoidoscopic examinations. Repeated search for parasites in the stools was negative, as were blood cultures and serologic tests. After four weeks he was discharged essentially unimproved, having lost 30 pounds. He remained at home on restricted activity, with persistent, nonbloody diarrhea (five or six movements daily). A year later an exacerbation sent him to another hospital for three months. By the time of discharge the diarrhea had subsided, and he had regained the weight lost. He then worked as a taxi driver for six weeks before another exacerbation sent him home, where he remained a chronic and neglected invalid until a month before admission. At that time, with the onset of an upper respiratory infection, the diarrhea became worse, and the patient's general condition deteriorated rapidly. Anorexia, edema, weakness and severe perianal inflammation developed. The weight fell from 125 to 85 pounds.

Physical examination disclosed a pale and emaciated patient with a moderate pitting edema up to the axilla. He lay incontinent in bed, discharging semisolid stools frequently. The skin was dry, shiny, tender and red over both femoral trochanters. Severe inflammation with multiple draining abscesses surrounded the anus. The tongue was abnormally reddened, with irregular patches of denudation of the epithelium. The prepuce was edematous. There was dullness over the right lung base, and the breath sounds were diminished. The abdomen was tense but not tender. The area of liver dullness extended 2 cm. below the costal margin.

The temperature was 98°F., the pulse 92, and the respirations 22. The blood pressure was 90 systolic, 60 diastolic.

Examination of the blood revealed a red-cell count of 3,700,000, with a hemoglobin of 8 gm. per 100 cc., and a white-cell count of 8500, with 66 per

cent neutrophils. The urine had a specific gravity of 1.026, with occasional white cells in the sediment, and examination was negative for albumin, sugar, red cells and casts. Guaiac tests on the stools were strongly positive. The total serum protein was 3.67 gm., and the nonprotein nitrogen 22 mg. per 100 cc.; the sodium was 140.3 milliequiv., and the chloride 102 milliequiv. per liter. An x-ray film of the chest showed a small amount of fluid on each side, with a few linear areas of density in the lingula of the left upper lobe.

In the hospital the patient's condition was consistently unsatisfactory. On the fourth hospital day massive swelling of the scrotum, penis and legs had developed, along with generalized itching and a pink papular rash on the abdomen and legs; the administration of 3 gm. of sulfadiazine daily was begun. A single whole-blood transfusion was given each day for five days, and the hemoglobin increased to 12 gm. per 100 cc. After the fifth transfusion the patient suffered a chill, and the temperature rose to 100.8°F. Within the next twenty-four hours the urinary output fell from a former level of 1750 cc. to 750 cc.; it remained low for several days, gradually returning to a level of 2250 cc. by the fourteenth day. The urine gave a + test for albumin on the fourth day and a ++++ test on the ninth. Thereafter, the test was +++ to ++++, the reaction was acid, and the specific gravity was between 1.004 and 1.014. The sediment on numerous occasions had 5 or 6 white cells, occasional red cells and 0 to many hyaline casts per high-power field.

Doses of 200 cc. of human serum albumin were given daily for nearly two weeks. The total protein rose from 3.67 to 4.42 gm. per 100 cc., with an albumin-globulin ratio of 1.56. Other treatment consisted of vitamins, 10 per cent Amigen, dextrose in water and courses of sulfapyridine and, later, penicillin. The diarrhea persisted. For many days the patient was markedly edematous despite the daily output of 2000 to 2500 cc. of urine, which contained from 23 to 45 gm. of protein on numerous determinations. He had satisfactory diuresis only after the administration of acacia, a total of 150 gm. having been given. The temperature ranged between 99 and 101°F.

X-ray examinations of the chest continued to show small to moderate amounts of fluid, with occasional areas of density and haziness suggesting consolidation or multiple infarcts. Toward the end of the second hospital week the abdomen became diffusely tender and remained so for several days.

During the first month the serum protein level was usually about 4 gm., and the nonprotein nitrogen 20 to 24 mg. per 100 cc. A phenolsulfonephthalein test on the twenty-fifth day showed 25 per cent excretion of the dye in thirty minutes and 60 per cent in two hours. A Congo-red test at about that time showed 33 per cent retention of the dye in the serum.

Mercupurin was given after the supply of serum albumin ran out. The edema gradually diminished and the temperature approached normal, but the patient remained extremely ill. The sinuses about the anus continued to drain. On the forty-fifth hospital day an ileostomy was performed. Postoperatively intractable small-bowel distention developed. The urine output fell to 200 cc. over a seven-day period, and the nonprotein nitrogen rose to 150 mg. per 100 cc. The insertion of a Miller–Abbott tube failed to improve the distention. The chloride fell to 76 milliequiv. per liter. Terminally there was anuria for thirty-six hours. Hyperpnea and involuntary movements developed, and death occurred on the fifty-fourth hospital day.

Differential Diagnosis

Dr. Marian W. Ropes: In this patient there were surely two major sites of disease — the gastrointestinal tract and the genitourinary tract. As I see it, the problem is to decide the nature of the two diseases, whether they were interrelated and, if so, in what manner. So far as the gastrointestinal disease is concerned, the history, in general, is consistent with that of chronic idiopathic ulcerative colitis. Unfortunately we are not told anything about the results of proctoscopic or x-ray studies, but we are told that they were consistent with this disease at least during the first attack. It would be of interest to know if these studies were repeated during the second attack and, if so, what the findings were.

Dr. Harold E. Elrick: Barium-enema and proctoscopic examinations were not done.

Dr. Ropes: I assume that the findings in the first attack corroborated the diagnosis and that the findings in the terminal attack were similar. There are some unusual features, however. The degree of perianal inflammation with many draining abscesses is unusual; this is not inconsistent with the diagnosis, however, and does not make it necessary for us to consider seriously other possible causes of ulcerative colitis, such as tuberculosis. The degree of edema seems definitely more than one would expect in such a patient with ulcerative colitis, particularly since the edema apparently persisted and possibly increased, although it is difficult to be sure of that, since the serum protein rose to 4.5 gm. per 100 cc. If the edema had been on a purely nutritional basis it would have been unusual for it to fail to respond to the administration of albumin, with its resulting elevation of the serum protein, and subsequently to respond to acacia. In addition, the pulmonary changes were not characteristic.

May we see the x-ray films?

Dr. Tracy B. Mallory: The X-ray Department sent the report over that there was no point in showing the films, which add nothing to what is given in the record.

DR. ROPES: The fluid in the pleural cavities is consistent with a generalized anasarca. The small areas of consolidation varying from time to time are difficult to interpret; I think that they were not specifically related to the underlying gastrointestinal or genitourinary disease. The changes in the skin and tongue were in general consistent with the nutritional disturbance. That is not true of the rash, and I find no explanation for the itching and rash, which were probably associated, other than the possibility of some medication that we do not know about. Clubbing of the fingers, I judge, was not present. I should have thought that it would have been after five years of ulcerative colitis.

DR. ELRICK: It was present.

DR. ROPES: Apparently, there were no joint symptoms, which might have been expected, since joint involvement is not too rare in ulcerative colitis. The abdominal tenderness in the second week is consistent with the degree of tenderness seen in uncomplicated ulcerative colitis, but the suddenness of onset suggests the possibility of a small perforation, which I consider unlikely, however. Similarly, the ileus, with the small-bowel obstruction and distention that occurred following operation, could have been secondary to the disease itself but suggests the possibility of superimposed peritonitis. In general, therefore, the gastrointestinal involvement is consistent with chronic ulcerative colitis — but not the genitourinary involvement.

Several possibilities should be considered regarding the genitourinary difficulties. As I have said, the degree of edema was out of proportion to what one would expect in a patient with ulcerative colitis at that stage. It suggests a nephrotic state. There is little evidence that this could have been the nephrotic state of chronic nephritis, although it is impossible to rule out nephritis. The onset of the acute illness following a respiratory infection and the sudden downhill course suggest that diagnosis, but the findings are somewhat against it. On the other hand, the urinary findings, with the high albumin in the absence of cells and the presence of only a few or a moderate number of casts, the nephrotic picture, the low nonprotein nitrogen until the terminal stage and the relatively good phenolsulfonephthalein excretion are typical of amyloid disease of the kidney.

Another possibility to be considered is whether or not sulfonamide treatment or transfusion reaction caused any of the renal damage in this patient, as suggested by the few signs of renal involvement at the time of admission and the marked changes after sulfonamide treatment had been started and after the transfusion reaction. On the other hand, such marked changes without elevation of the nonprotein nitrogen lasting for a long period are unusual in kidney damage due to either of these factors alone. Therefore, I think that amyloid involvement of the kidney is the most probable explanation of the renal disease. If so, it is interesting, because such involvement in ulcerative colitis is, I think, extremely rare. I know of only one case in the literature — that reported by Moschcowitz,* ten years ago. The serum globulin, which is frequently high in the diseases to which amyloid is secondary, was definitely low in this patient — below 2 gm. per 100 cc. The liver enlargement is consistent with amyloid disease but is not greater than what one would expect with ulcerative colitis of this severity. If amyloid disease caused the renal involvement, the question arises whether sulfonamide treatment or a transfusion reaction hastened the renal failure. I think that this is impossible to answer clinically. I have been impressed, however, with the course of two patients with amyloid disease of the kidney who died here fairly recently. Both went rapidly into renal failure with marked urinary changes, and in both sulfonamides or penicillin had been given before the changes occurred. I have no idea whether or not the sulfonamide treatment or transfusion reaction was related to the renal failure in this patient.

If this patient had amyloidosis secondary to ulcerative colitis, it is of interest that amyloidosis is not a rare complication of rheumatoid arthritis and that rheumatoid arthritis is often associated with ulcerative colitis. In the hospital at the present time we have a woman with probable rheumatoid arthritis, acute ulcerative colitis and amyloid disease.

In putting this picture together, therefore, I shall conclude that this patient had chronic idiopathic ulcerative colitis, with secondary amyloid disease involving at least the kidneys. Whether the liver was also involved, I do not know, although it is probable that it was. I do not know whether the sulfonamide treatment or transfusion reaction further damaged a kidney in which amyloid disease was already present.

DR. JOSEPH C. AUB: Would Dr. Ropes like to suggest that this man had amyloid disease of the small intestine?

DR. ROPES: We have had a great deal of discussion regarding whether or not amyloid disease gives active clinical disease of the gastrointestinal tract. There is no question that amyloid can be deposited in the gastrointestinal tract. The clinical symptoms arising from this amyloid involvement are apparently rare. We have a patient in the hospital with amyloidosis and small polypoid masses in the lower gastrointestinal tract, one of which has been biopsied. I do not know the result.

DR. AUB: I have seen amyloid disease with involvement of the whole small intestine.

DR. ROPES: With symptoms?

DR. AUB: I cannot remember.

DR. CHARLES H. BURNETT: We were perplexed in the same way about the renal situation and the

*Moschcowitz, E. Clinical aspects of amyloidosis. *Ann. Int. Med.* 10: 73-88, 1936.

sudden appearance of the nephrosis. A single examination of the urine was negative on admission, with the subsequent appearance of albuminuria following the administration of sulfonamides and blood. There was no evidence of a hemolytic reaction. And although a transfusion reaction was ruled out, we did not know what the influence of the sulfonamides was. We were strongly enough impressed to stop the sulfonamides, however.

DR. ROPES: I neglected to mention the Congo-red test, which I thought was confirmatory evidence of amyloidosis. Retention of 67 per cent of the dye in the tissues, leaving only 33 per cent in the serum, is certainly presumptive evidence of the presence of amyloid.

DR. BEVERLY TOWERY: Is there any evidence that Amigen or acacia influences amyloid disease?

DR. ROPES: I do not know whether acacia does, but the repeated injection of sodium caseinate is one of the best ways of producing the disease experimentally in animals.

CLINICAL DIAGNOSES

Chronic ulcerative colitis.
Nephrotic syndrome.
Amyloid nephrosis?
Postoperative ileus.

DR. ROPES'S DIAGNOSIS

Chronic idiopathic ulcerative colitis, with secondary amyloidosis.

ANATOMICAL DIAGNOSES

Ulcerative colitis.
Amyloid degeneration of kidneys, liver, spleen and adrenal glands.
Operation: ileostomy, recent.
Pulmonary embolus, with infarction of lung, small.
Organizing thrombus of both common iliac arteries and inferior vena cava.

PATHOLOGICAL DISCUSSION

DR. MALLORY: At autopsy the peritoneal cavity was perfectly clean. There had been no peritonitis or mechanical obstruction following the ileostomy, and the dilatation of the small bowel must have been of a reflex origin. The entire large bowel was involved in a severe ulcerative process. The mucosa was markedly atrophied but showed an occasional bridge of mucosa across an area of ulceration. There was no ulcerative process in the ileum. Although the wall of the terminal segment of the ileum was edematous and thickened, it showed no amyloid. The liver was large, weighing 2500 gm., and was somewhat pale but not yellow or greasy and, we thought, not significantly fatty on gross examination; it was firmer than normal, and the markings were unusually prominent. We suspected amyloid, which was borne out by the histologic examination — in fact, there was rather extensive involvement in the liver. The spleen was large and showed typical sago bodies characteristic of amyloid deposits in the malpighian corpuscles. The kidneys were markedly swollen, their combined weight being 600 gm.; the cortex was extremely pale and thickened to 9 or 10 mm.

DR. WADE VOLWILER: Did the acacia still remain in the organs?

DR. MALLORY: It is not easy to see; I could not pick it out. The kidneys, as far as I could determine, represented a pure amyloid nephrosis. There were only moderate deposits of amyloid in the glomeruli but marked secondary degeneration of the tubules, especially the proximal convoluted tubules, as well as markedly dilated lumens containing a great deal of precipitated protein and much swollen epithelium. There was nothing to suggest a hemoglobinuric nephrosis or, so far as I could see, sulfonamide reaction.

There was a small pulmonary embolus, with a corresponding area of infarction, in the right lower lobe. The source of the embolus was a large thrombus that had almost completely occluded the lower 15 cm. of the inferior vena cava and both common iliac veins.

As Dr. Ropes pointed out, amyloid is an unusual complication of ulcerative colitis. I cannot remember having seen it before.

DR. AUB: Was there any amyloid in the small intestine?

DR. MALLORY: No; there was, however, severe amyloid disease of the adrenal glands — enough to make me wonder if the patient had had adrenal insufficiency.

A PHYSICIAN: Were anaerobic cultures made of the fluid draining from the anal sinuses?

DR. MALLORY: No effort was made to culture the pus. Such sinuses are not a rare complication of idiopathic ulcerative colitis. They sometimes extend quite a distance on either side of the anus. We have seen cases in which both buttocks were almost completely destroyed.

CASE 33022

PRESENTATION OF CASE

First admission. A sixty-three-year-old postal clerk entered the hospital because of pain and numbness of the feet and shoulders.

Fourteen years before admission the patient was found to have had glycosuria without hyperglycemia. Two years later he entered a hospital because of hematuria. Diagnoses of diabetes mellitus and ureteral stone were made, and a right ureterolithotomy was performed. At the time of discharge the blood sugar was normal, and there was no glycosuria. For the following twelve years the patient was well. He took no insulin and ignored his diet. Five months before admission, on the way home from work he became dizzy, felt tired and

weak, noted palpitation and found it difficult to breathe. There was a sense of substernal oppression but no pain. A physician found a blood pressure of 230 systolic, 140 diastolic, albuminuria and glycosuria. The face was swollen. The patient remained in bed for twelve days with orthopnea and vague generalized abdominal pain; he also had a severe frontal headache, dizziness and black spots before the eyes. Vague pains and numbness on the dorsal surfaces of the feet and in the right shoulder were observed at the same time. These symptoms, which persisted and increased during the succeeding months, constituted the chief complaint on admission. Four and a half months before admission the patient was admitted to another hospital. Albuminuria was marked; the fasting blood sugar was 170 mg. per 100 cc. The nonprotein nitrogen was normal, and an intravenous pyelogram showed 34 per cent excretion of the dye in one hour. Red and white cells were found in the urinary sediment. The patient was discharged in ten days still not improved. There were persistent hematuria and a weight loss of 14 pounds. He was taking 14 units of protamine zinc insulin daily. Two weeks later he felt sufficiently improved to go back to work. Blurring of vision and pain in the feet and shoulders persisted. Two and a half months later follow-up examination at the same hospital showed the blood pressure to be 194 systolic, 78 diastolic, and the nonprotein nitrogen to be 74 mg. per 100 cc. Thereafter he was followed in the Out Patient Department of this hospital, where the blood sugar levels were found to be 135, 149 and 258 mg. per 100 cc. on different occasions. There were a moderate anemia and a moderate leukocytosis, as well as a carbon dioxide combining power between 23.5 and 25.8 milliequiv. per liter.

Physical examination on entry showed an apical systolic murmur; the aortic second sound was louder than the pulmonic. The blood pressure was 172 systolic, 98 diastolic. There were small hemorrhages in both fundi, and a few whitish exudates were seen. The lungs were normal. Pulsations were felt in all the main arteries of the lower extremities, and oscillographic abnormalities were minimal. Neurologic examination showed only a slight decrease in vibration and position sense in the lower extremities. The knee and ankle jerks were hyperactive but equal.

Examination of the blood revealed a red-cell count of 3,300,000, with a hemoglobin of 70 per cent. The urine gave a ++ test for albumin. The urinary sediment contained occasional white cells and 4 or 5 red cells per high-power field, with rare hyaline and finely granular casts. Cultures of the urine showed no growth. The phenolsulfonephthalein test showed 17 per cent excretion of the dye in one hour and 24 per cent excretion in two hours. The nonprotein nitrogen was 66 mg., and the fasting blood sugar 135 mg. per 100 cc. The urine sugar reactions were consistently green. Plain films of the abdomen showed the kidney outlines to be indistinct; the left kidney appeared normal, and the right was not definitely visible. On an x-ray film of the chest the heart did not appear definitely enlarged. Films of the feet showed slight calcification of the dorsalis pedis arteries. An electrocardiogram taken shortly after admission demonstrated slightly sagging ST segments in I eads 1, 2 and 3, a depressed ST_4, and a sharply diphasic T_4. The rhythm was normal.

Treatment consisted of warm foot baths, massage and exercises. The pain and numbness in the lower extremities rapidly disappeared. On the fourth and sixth days the urine contained many red cells, but there was no other outward incident in the twelve-day hospital stay.

Final admission (six years later). After discharge the patient was followed in the diabetic clinic, where the blood sugar was normal and glycosuria was absent. He was taking 16 units of protamine zinc insulin daily and was following his diet. On the last visit to the clinic, five years before admission, the nonprotein nitrogen was 38 mg. per 100 cc. The patient was fairly well until a year before admission, when he began to notice severe progressive weakness, dyspnea and failing vision. He was given digitalis by a physician, but the symptoms continued. He also suffered from urinary difficulty with nocturia and frequency. For several weeks before admission he had been confined to bed. Five days before admission he developed an epistaxis, which persisted and brought him to the Emergency Ward.

Physical examination showed an emaciated, pale and weak man who was bleeding profusely from the right nostril and gagging from blood clots in the nasopharynx. During the examination he vomited 60 cc. of clotted blood. The pupils were small, but reacted to light and accommodation. The neck veins were distended, and the heart enlarged, extending 10 cm. to the left of the midsternal line in the sixth interspace. There were no murmurs. There were rales at the bases of both lungs. The liver edge was palpable 4 cm. below the costal margin. The bladder was felt 4 cm. above the symphysis. There was thickening of the epididymis. The prostate was symmetrically enlarged and indurated. There was moderate pitting edema of the ankles and legs.

The temperature was 98.8°F., the pulse 105, and the respirations 20. The blood pressure was 160 systolic, 90 diastolic.

Examination of the blood revealed a red-cell count of 2,050,000, with a hemoglobin of 7 gm., and a white-cell count of 12,300, with 90 per cent neutrophils. The specific gravity of the urine was 1.004. The sugar reaction was green. On admission there was no albumin, but on the next day there was a ++++ test for albumin. The sediment was reported to contain innumerable bacteria.

The bleeding was stopped shortly after entry, and a whole-blood transfusion was administered. Two

days later the nonprotein nitrogen was 70 mg., and the fasting blood sugar 132 mg. per 100 cc. The carbon dioxide combining power was 27.1 milliequiv. per liter. The chloride was 106 milliequiv. per liter, and the total protein 6.4 gm. per 100 cc.

The nonprotein nitrogen level doubled in two days, reaching 145 mg. per 100 cc., whereas the carbon dioxide dropped to 25 milliequiv. per liter. The patient became comatose and died on the fourth hospital day.

Differential Diagnosis

Dr. Charles L. Short: In the first place, we must assume that this patient had diabetes on the basis of the history and the laboratory findings. This diagnosis was first made eighteen years before final admission, but he was under treatment for only six years. The diabetes was complicated at one point by neuritis, which was symptomatically relieved by therapy, and eye-ground changes consistent with diabetic retinopathy. The patient died in cardiac failure, the heart disease evidently being secondary to the long-standing high blood pressure. The episode five months before the first admission, when he suddenly developed weakness, dyspnea and palpitation, suggests a coronary occlusion, although he did not have actual pain. The clinical picture, however, and the electrocardiogram do not seem characteristic of that condition.

The real problem, it seems to me, is to determine the nature of the renal lesion. We might briefly recapitulate the course of the kidney disease at this point. Eighteen years before admission the patient had hematuria and a right ureteral calculus was removed, but no note is made of the blood pressure at that time. About twelve years later, he was found to have albuminuria and severe hypertension, so that there is no clue regarding whether the hypertension preceded the renal disease or vice versa. At the time of the first admission, red cells and casts were found in the urinary sediment, and nitrogen retention had already been noted. X-ray studies disclosed a left kidney that seemed to be of normal size, but the right kidney was not visible. Since the x-ray films are not here, I shall assume that they add nothing to the written report. I do not believe that we can draw any conclusion from the failure to see the right kidney; it may simply have been obscured. At that time the patient again showed marked hematuria; he was apparently well for five years, and the kidneys regained adequate function, since the nonprotein nitrogen was normal. A year before death he developed cardiac failure and finally uremia, which presumably accounted for the anemia and bleeding. At the final admission he continued to have albuminuria, and the sediment for the first time contained many bacteria.

A number of types of Bright's disease can produce a terminal picture of hypertension and uremia. I do not need to list them all, but I shall mention some of them in the differential diagnosis. Since this patient was diabetic, one thinks of the renal lesion associated with diabetes — namely, intercapillary glomerulosclerosis. It would be hazardous to say that this condition was not found to some extent histologically in this patient, since certain authors report its presence, to some degree, in at least half the diabetic patients at autopsy. Slight glomerulosclerosis may also be found in nondiabetic patients. I hope that Dr. Mallory will comment on this point later. We are trying to determine the important cause for the renal failure, and I am therefore going to discard this condition as having been primarily responsible, chiefly because at no time did the patient present the nephrotic picture that is often associated with severe degrees of intercapillary glomerulosclerosis. The fact that he once had swelling of the face may represent renal edema, but I do not believe that we are justified in making this diagnosis merely because the patient was diabetic. Swelling of the face is suggestive of glomerulonephritis, but there was no definite history of an acute attack, so that we have no knowledge that the kidney disease preceded the hypertension. Nephrosclerosis or vascular nephritis is probably as good a bet as any, and in any event autopsy probably showed arteriolar changes in the kidneys in view of the long-standing hypertension As a fundamental cause of the renal insufficiency, however, I am more in favor of a condition that has been recognized accurately only in recent years as an important cause of kidney disease and hypertension. I refer to pyelonephritis, which, in a chronic or healed stage, may result in the terminal picture shown by this patient. The ureteral calculus eighteen years before death may have been highly significant, either as a primary cause of obstruction and infection or on the basis of a preceding infection. It is true that the patient gave no history of an acute pyelonephritis, but such a history is not elicited in most cases. The urinary sediment showed no definite evidence of infection until just before death. Cultures at the first admission were negative, but the process may have been relatively quiescent or healed at that time. The hematuria, which may also have been due to recurrent urinary calculi, is sometimes prominent in this form of nephritis. Pyelograms at the first admission would have been helpful and perhaps diagnostic, although cases of pyelonephritis have been reported with negative x-ray findings. The fluctuation in the course of the disease and the return of adequate function after uremia had set in are compatible with pyelonephritis. At the final admission the nocturia and frequency, the urinary picture, the prostatic hypertrophy and the enlargement of the bladder suggest that another factor was involved in the last part of the illness — namely, an obstructing prostate with infection behind it. I realize that this is a somewhat slender chain of evidence, but chronic or healed pyelonephritis is my first choice.

In addition, the patient had diabetes and hypertensive heart disease, with cardiac enlargement and failure.

DR. JACOB LERMAN: How do you explain the electrocardiographic findings unless he was taking digitalis or had a coronary infarct?

DR. SHORT: I am not an electrocardiographer, but I believe that this patient's tracing was not specific for coronary disease; it may have been compatible with hypertension or myocardial disease and could have followed the administration of digitalis.

CLINICAL DIAGNOSES

Hypertensive heart failure.
Uremia.
Diabetes mellitus.

DR. SHORT'S DIAGNOSES

Chronic pyelonephritis.
Diabetes.
Hypertensive heart disease, with cardiac enlargement and failure.

ANATOMICAL DIAGNOSES

Chronic glomerulonephritis, inactive.
Cardiac hypertrophy.
Coronary sclerosis.
Chronic passive congestion.
Benign hyperplasia of prostate.
(Diabetes mellitus.)

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: It is always a difficult clinical problem to decide what type of renal insufficiency will be found in a case of this sort. Sometimes, it is equally difficult or even quite impossible after one has seen the results of post-mortem examination. Dr. Short decided to rule out intercapillary glomerulosclerosis — the Kimmelstiel–Wilson syndrome* — and was correct in so doing. A small number of glomeruli in the kidney showed slightly suggestive changes, but no more than one might find in any diabetic patient. That certainly was not the major cause of the trouble. The kidneys were markedly contracted, their combined weight being only 100 gm. The surface was pitted and scarred, and the cortex was reduced to 2 mm. in thickness. On microscopic examination the outstanding phenomenon was that almost every glomerulus was surrounded by a crescent of collagen that lay within and obliterated Bowman's capsule. I do not see how this could have been produced except by a capsular glomerulonephritis. The epithelial cells lining the capsule first proliferate and later give way to fibroblasts, which lay down collagen. I am therefore quite content in this case to commit myself to a diagnosis of old chronic glomerulonephritis. I think that it is still within the limit of possibility that other pathologists would interpret this case differently. The patient had the basis for a pyelonephritis in the form of a hypertrophied prostate, cystitis, dilatation of the ureters and slight dilatation of the pelves of the kidneys.

The heart was enlarged, presumably secondarily to the hypertension. The coronary arteries were markedly sclerotic and narrow but not occluded at any point. The myocardium, particularly the interventricular septum, showed slight patchy discoloration on gross examination and slight focal degeneration on microscopic examination. There was not, however, any significant area of infarction. The lungs and the liver both showed severe chronic passive congestion.

In a case of chronic renal insufficiency we always look with interest at the parathyroid glands. The first person who searched for them in this case did not find them, which I think is evidence that they were not markedly enlarged. Dr. Castleman made a secondary search and found two glands of normal size and a tumor nodule measuring 1.0 by 1.5 cm. This turned out to be an interesting curiosity. The sections showed the characteristic picture of a fetal lung, with well formed bronchi and alveolar spaces lined with cuboidal epithelium. This is an infrequent but not extremely rare congenital anomaly. One hardly expects to find it in a seventy-year-old man, however, or as high in the neck as this one was. When bronchial buds grow into extrapleural tissues a small growth of lung tissue may occur, but since the lesion is extrapleural, it never expands and maintains the character of a fetal lung. In this case it was a coincidental lesion of purely pathological interest.

*Kimmelstiel, P., and Wilson, C. Intercapillary lesions in glomeruli of kidney. *Am. J. Path.* 12:83-98, 1936.

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A NEW RICKETTSIAL INFECTION IN NEW YORK CITY

During June and July, 1946, there appeared in New York City a peculiar febrile disease that aroused considerable interest and had both clinicians and laboratory workers temporarily baffled. The disease affected 92 residents of Kew Gardens in the Borough of Queens and 10 other persons elsewhere in New York City.[1-3]

The illness was clinically characterized by an initial skin lesion on some part of the body. This appeared as a papule with surrounding erythema, was round or oval in shape and about 0.5 to 1.0 cm. in diameter. Coincidentally the regional lymph nodes became enlarged and sometimes slightly tender. The patients, however, usually did not feel sick, and they continued to work until five to ten days later, when there was an acute onset of chills, fever, sweating, headache and backache. The chills were often repeated several times a day, with temperature rises to between 102 and 104°F. and remissions to 99 or 100°. The headache was usually quite severe. About three or four days after the onset of these symptoms a rash appeared over the body. The individual lesions were maculopapular and varied from 2 to 5 mm. in diameter; some were flat, others somewhat pointed. Frequently, a deep-seated vesicle was seen in the center of the lesion, which often broke down and formed a crust. The fever, rash and other symptoms usually lasted from four days to a week. Although the patients felt sick, they did not usually appear particularly toxic at any time during the entire illness. The spleen was palpable in about half the cases but was never large.

Laboratory examinations were of no great help. The urine was usually normal. White-cell counts showed a leukopenia, with either a normal differential count or a lymphocytosis. Blood cultures were sterile. There was no increase in heterophil antibodies. The serums in both the acute and the convalescent stage showed no agglutination of typhoid and paratyphoid bacilli, the organisms causing brucellosis and tularemia, Proteus X-19 or leptospira. Complement-fixation tests were negative for typhus fever, Rocky Mountain spotted fever, Q fever, scrub typhus and psittacosis.

Epidemiologically the cases were interesting because the majority of them were reported from one group of buildings in a section of Kew Gardens. Although the physicians who saw these cases had patients in other buildings in the immediate neighborhood and in areas nearby, they saw no other cases. Single cases, however, were observed by physicians of the New York City Department of Health in Manhattan and in the Bronx.

There were no fatalities, and no complications were observed in any of the cases. The disease did not respond to antibiotic or other specific therapy, and most of the cases were treated symptomatically.

The entire picture of the disease strongly suggested a rickettsial infection, and since all the tests for known diseases were negative, the aid of the National Institute of Health was enlisted. As a result, a

collaborative study by members of the New York City Department of Health and by Drs. Heubner and Armstrong of the National Institute of Health was undertaken.

At the National Institute of Health, an organism was isolated that possessed the morphologic, cultural and staining characteristics of the rickettsias.[4] This organism was recovered from the tissues of a single mouse, which had been inoculated with blood drawn on the second day of fever from one of the patients. It produced illness in mice and guinea pigs and grew well in the yolk-sacs of fertile eggs. Ether extract yolk-sac antigens were then prepared, and these were shown to fix complement when mixed with serums drawn from convalescent cases. This complement-fixation reaction was apparently specific so far as it was tested, except for cross reactions with serums from patients with Rocky Mountain spotted fever.

The agent was also isolated from a saline suspension of tissues of mites (*Allodermanyssus sanguineus*) collected in the house of the patient from whose blood the original rickettsia was obtained,[5] and a similar rickettsia was recovered from a mouse that was bitten by one of these mites. The strains isolated from the mite and from the mouse were identical with the one obtained from the patient. The identity of the strains was also established by the fact that each established a solid cross immunity in guinea pigs.

Because of the vesicular appearance of some of the lesions, the disease was called "rickettsialpox," and since the agent was isolated from mites, it was named *Rickettsia akari*, after the Greek name for mite. The recovery of apparently identical strains of rickettsia from the blood of a man ill with rickettsialpox and from blood-sucking mites collected from the home of the same man indicate that human infection was acquired from the mites, probably through biting.

The increase in the frequency with which Q fever has been observed in this country and the isolation of this new strain of rickettsia from a case of an entirely different type of disease in New York City both point to the increasing importance that rickettsias are assuming as causes of disease in the United States.

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THE MEANING OF PSYCHOSOMATIC MEDICINE

CURRENT medical literature is marked by the number of articles on psychosomatic medicine. Although this is an indication of a healthy interest in the relation between psychic and somatic factors, which pervade sickness of all kinds, some of these articles suggest that there is occurring a subtle revision of the original meaning of the term "psychosomatic," which, if it becomes established, may do great harm. This is a matter of general interest and of basic significance.

When the term was first promulgated it was on the basis that disease of whatever kind always included in its manifestations elements of both somatic and psychic origin. Although the bodily aspect might have been in some cases the precipitating cause, it was thought that psychic disturbances always were included in the complete pattern of the disorder. In the same way, when psychic factors dominated the inception of an illness somatic disturbances always occurred and contributed their part to the manifestations of the disorder. Psychosomatic medicine therefore meant that disease is never wholly somatic or entirely psychic: it is always, with certain limitations, a combination of both. To emphasize the absence of a dichotomy between the somatic and psychic factors the term was put forth with the hope that it would no longer be necessary to say, with Kennedy,[1] that, "lacking appreciation of the neurological aspect of all disease, for it must color all by pervading all, we must perforce regard our patients not as persons but as congeries of viscera imperfectly combined and inadequately framed in design."

What is happening to the term "psychosomatic" seems to be a revision of definition that makes it mean something quite different from what it did

originally. Thus, Menninger[2] implies that what he means by psychosomatic medicine comprises the organ neuroses. It is not likely that he intended to give quite this impression, but his article serves as an illustration of a growing tendency to limit, if not to redefine, the term. Such a redefinition would restrict the term to those disorders that are thought to be psychic in origin and somatic in manifestation. This does not appear to conform to the original meaning: it is a revision, if not a distortion.

Not only does this alteration warp the conception so well presented by Dunbar[3] in her book *Emotions and Bodily Changes*, but it threatens to undo the good work that she initiated. The former rigid classification of disease as either somatic or psychic is no longer tolerable in the light of present-day concepts. Dunbar's book pointed this out and set the course of medicine in the proper direction. It is regrettable that through misunderstanding or lack of clarity so many writers are upsetting the concept that all disease is both somatic and psychic. Restriction of the term "psychomatic" to the somatic manifestations of psychic disorders will, if it persists, materially delay general realization of the true nature of disease and will necessitate the classification of disease as somatic, psychic and psychosomatic. This would be regrettable.

Many examples of this process of revision could be given. With characteristic enthusiasm, clinicians seem to be forming a cult, glibly using the latest catchword without taking the trouble to understand its meaning. It might even be better if psychosomatic were abandoned and the simple word "sick" or some synonym were to be used. If it were understood that to be sick is to be assailed by influences derived from and expressing elements of both mind and body, the clinician might find it less convenient to fit the condition of the patient into any rigidly defined category. It would then be easy and natural to regard the patient as a person, as suggested by Robinson,[4] and to look for all the elements that go to form the complex of his disease. It would also be easy and natural to realize that what often passes for mental disease is quite likely to result from organic causes and that organic expressions of disorder often result from psychic causes. Beyond all this it would be both easy and natural to realize that all disease is compounded of both bodily and mental factors.

One of the great medical achievements of the past few years has been the recognition of the part played by the emotions in disorders that were previously regarded as solely organic. Perhaps an achievement of equal importance will come from the realization of the part played by organic factors in what now is considered to be solely mental disease. If it is too late to undo the harm caused by the subtle revision of the term "psychosomatic" then it may be necessary to devise an alternative. Thus, if psychosomatic is to be confined to organic disorders arising from psychic causes, then it may be counteracted by some such term as "somatopsychic" to be used in connection with mental diseases of somatic origin. It is hoped that no such clumsy circumlocution will be needed. No occasion for it will exist if the original meaning of psychosomatic is not distorted. After all, this word obviously was introduced in this form for the sake of euphony and not because of any design ascribing to one factor priority over the other.

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MASSACHUSETTS MEDICAL SOCIETY

DEATH

KANE — WILLIAM V. Kane, M.D., of Lynn, died October 11. He was in his fifty-fifth year.

Dr. Kane received his degree from Tufts College Medical School in 1915. He was a member of the New England Pediatric Society.

MISCELLANY

"DOCTORS — THEN AND NOW"

The 1946–1947 program of broadcasts sponsored by the American Medical Association and the National Broadcasting Company will trace the highlights in medical progress in the United States since pioneer days. The whole country has been divided into twenty-five sections, and in each a dramatization of some local event that contributed to the advance of medical knowledge will be given. Thus, in the section composed of Massachusetts, Rhode Island and Connecticut the story will concern Oliver Wendell Holmes's contribution to the conquest of puerperal fever and his coining of the word "anesthesia," whereas in Maine, New Hampshire and Vermont the story will be based on Nathan Smith's efforts that led to the formation of highly successful medical schools at Dartmouth College, Yale University, Bowdoin College and the University of Vermont. At the close of each dramatization the program will conclude with up-to-the-minute news of what is now being done in each particular section to further medical knowledge, to promote public

health and to improve medical care; these facts will be presented by an official representative of the state medical society.

The broadcasts should accomplish much in informing the public concerning the remarkable advances in medicine that have been made during the last hundred years and the facilities that are now available to raise the health standards of the Nation, and they are, of course, particularly appropriate for the centennial year of the American Medical Association. The first was given from 4:00 to 4:30 p.m. (EST) on Saturday, December 7, and one has been given or is scheduled on each following Saturday. The final broadcast, the twenty-sixth, will deal with the hundred years of the American Medical Association from a nationwide standpoint. To ensure a large radio audience, all physicians in each section are urged to publicize its program, the date of which will be published in the *Journal of the American Medical Association*.

NOTE

The following appointments to the teaching staff of Harvard Medical School were recently announced: Max Bovarnick, of Newton Highlands (A.B. Harvard University 1930, M.D. Harvard University 1934, Ph.D. Columbia University 1938), assistant professor of bacteriology and immunology; Grete Lehner Bibring, of Cambridge (M.D. University of Vienna 1924), associate in psychiatry; Seymour Jerome Gray, of Washington, D. C. (A.B. University of Rochester 1933, M.D. University of Pennsylvania 1936, Ph.D. University of Chicago 1945), assistant professor of medicine; Marian Cabot Putnam, of Milton (A.B. Radcliffe College 1917, M.D. Johns Hopkins University 1921), lecturer on psychiatry; DeWitt Stetten, Jr., of New York City (A.B. Harvard University 1930, M.D. Columbia University 1934, Ph.D. Columbia University 1940), assistant professor of medicine.

CORRESPONDENCE

CONVALESCENT HOMES

To the Editor: The Committee on Public Health Relations of the New York Academy of Medicine is preparing a new edition of the *Directory of Convalescent Homes in the United States*, to be published by the Sturgis Fund of the Winifred Masterson Burke Relief Foundation of White Plains, New York. The last issue of this directory was published by the Sturgis Fund in 1931 under the auspices of the Committee on Convalescent Care of the American Conference on Hospital Service and has long been out of print. The need of a new directory is recognized by all concerned.

Early in January, a questionnaire will be distributed to all recognized convalescent homes maintained by municipalities, counties or voluntary bodies. The information sought deals with the physical plant, the staff, the requirements for admission, the type of patients, therapy and such other matters as will make the directory a dependable guide for physicians who wish to refer their patients to institutions for convalescence. The questionnaire is so devised that it can be filled out with a minimum of effort. Convalescent homes that do not receive a questionnaire are urged to request one by writing to E. H. L. Corwin, Executive Secretary, Committee on Public Health Relations, New York Academy of Medicine, 2 East 103 Street, New York 29, New York.

E. H. L. Corwin, *Executive Secretary*
Committee on Public Health Relations
New York Academy of Medicine
2 East 103 Street
New York City

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Psychoanalytic Study of the Child. Volume 1 (1945). 8°, cloth, 423 pp. New York: International Universities Press, 1945. $6.00.

This is the first volume of a new series of studies on child analysis and child guidance. Various authors, in both America and Europe, report on many aspects of a pertinent problem. The book is designed for the specialist, and as a survey of the work now being carried on in psychoanalysis, as applied to children, can be fully recommended. Most of the papers are supplied with bibliographic references, and the work has been carefully edited.

Essentials of Neuro-Psychiatry: A textbook of nervous and mental disorders. By David M. Olkon, M.D., associate professor of psychiatry, University of Illinois College of Medicine. 8°, cloth, 310 pp., with 138 illustrations. Philadelphia: Lea and Febiger, 1945. $4.50.

The author presents an exposition on the principles involved in the psychiatric studies of mental disorders. The text is complete, with many illustrations and references to the literature. The volume is a sound contribution to the subject from a modern point of view. In spite of the fact that the book covers only three hundred pages, the material is surprisingly comprehensive and the author shows evidence of a thorough grasp of his subject.

Rorschach's Test. Volume II. *A Variety of Personality Pictures*. By Samuel J. Beck, Ph.D., head of Psychology Laboratory, Department of Neuropsychiatry, Michael Reese Hospital, Chicago, and associate professor of psychology, Northwestern University. With a foreword by Roy R. Grinker, M.D. 8°, cloth, 402 pp. New York: Grune and Stratton, 1945. $5.00.

This is the second volume of a study on the Rorschach test. In the first, the author gave details regarding the method used in testing. He now presents an interpretation of his findings, giving many case histories to illustrate his points. There is a careful evaluation of clinical material, with an analysis of the records. The book is well printed, and there is an extensive bibliography. It should be of value to other workers in the same field.

New Directions in Psychology toward Individual Happiness and Social Progress. By Samuel Lowy, M.D. With an introduction by Herbert Read. 8°, cloth, 194 pp. New York: Emerson Books, Incorporated, 1945. $3.00.

This volume is based on a series of lectures given by the author in Czechoslovakia between 1930 and 1936. He has had wide experience in European countries and more recently, in the last four years, in Great Britain, where he has been associated with the Czechoslovakian Center in Manchester. The author has analyzed a large number of patients from different countries, and his book reflects a careful evaluation of this material. Much of the text relates to the social aspects of psychiatry, and the author goes deeply into the philosophic principles of racial relations, tolerance, psychology and similar subjects associated with the problems of readjustment, particularly of displaced persons.

Manual of Diagnosis and Management of Peripheral Nerve Injuries. By Robert A. Groff, M.D.; and Sara J. Houtz, B.S. With an introduction by I. S. Radvin, M.D., John Rhea Barton Professor of Surgery, University of Pennsylvania School of Medicine. 8°, cloth, 188 pp., with 111 illustrations. Philadelphia: J. B. Lippincott Company, 1945. $8.00.

The subject is well covered by this brief monograph, the result of war experiences with patients having injuries to the peripheral nerves. The conclusions, in general, are sound. The simple line drawings, illustrating examination and various types of injury, are excellent. The format leaves a good deal to be desired. Although the subject is fully reviewed, it does not add much new material to knowledge of injuries of the peripheral nerves. Most physicians will not agree with the statement that electrotherapy, in facial paralysis, "can do more harm than good in maintaining muscle tone and assisting restoration of muscle action."

NOTICES

ANNOUNCEMENTS

Dr. Archie A. Abrams calls attention to the omission of his office address and telephone number from the current telephone directory. His office is at 1093 Beacon Street, Brookline, and the telephone number is ASPinwall 8951.

Dr. Stephen D. Peabody, who has returned from military service, announces the opening of his office for the general practice of medicine at 7 Cross Street, Wellesley.

SOUTH END MEDICAL CLUB

The next regular meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, January 21, at twelve noon. Dr. Franz J. Ingelfinger will speak on the topic "Developments in the Treatment of Peptic Ulcer and Its Complications."

Physicians are cordially invited to attend.

NEW ENGLAND PEDIATRIC SOCIETY

A meeting of the New England Pediatric Society will be held on Wednesday, January 22, in Boston.

PROGRAM

1:15 p.m. Luncheon at Vanderbilt Hall, Harvard Medical School (price, 70 cents).
3:30 p.m. Clinical presentation of patients. Amphitheater, Joseph H. Pratt Diagnostic Hospital. Members of the medical profession and students are invited to attend.
5:30 p.m. Refreshments at Longwood Towers.
6:30 p.m. Dinner at Longwood Towers (price, $2.00, including tax). Members and their guests are invited to attend.
7:30 p.m. Annual meeting. Longwood Towers.
7:45 p.m. The Management of Respiratory Diseases in Infants and Children. Longwood Towers. Dr. James L. Wilson, professor, Department of Pediatrics and Communicable Diseases, University Hospital, University of Michigan. Members of the medical profession and students are invited to attend.

ELLA SACHS PLOTZ FOUNDATION FOR THE ADVANCEMENT OF SCIENTIFIC INVESTIGATION

During the twenty-third year of the Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation, forty applications were received by the Trustees, twenty-nine of which came from the United States, the other eleven coming from different countries in Europe, Asia and North and South America. Twenty grants were distributed.

Applications for grants to be held during the year 1947–1948 must be in the hands of the Executive Committee before April 15, 1947. There are no formal application blanks, but letters asking for aid must state definitely the qualifications of the investigator, an accurate description of the research, the size of the grant requested and the specific use of the money to be expended. In their requests for aid applicants should state whether or not they have approached other foundations for financial assistance and what other sources of support are relied on for research. It is highly desirable to include letters of recommendation from the directors of the department in which the work is to be done. Only applicants complying with the above conditions will be considered. Applications should be sent to Dr. Joseph C. Aub, Massachusetts General Hospital, Fruit Street, Boston 14.

SCIENTISTS NEEDED FOR U.S.P.H.S.

Competitive examinations will be held early in 1947 for appointment to the Regular Corps of the United States Public Health Service, according to a recent announcement by Dr. Thomas Parran, Surgeon General. Seventy-five vacancies exist in grades of assistant and senior assistant scientist.

Written examinations, covering each candidate's particular field of science, as well as related fields, will be held April 14 and 15 at places mutually convenient to the applicant and the Service. Oral examinations will be held during the period February 13–April 9 in thirty cities, strategically located throughout the United States. (The oral examination for candidates from New England will be held in Boston at the Marine Hospital, 77 Warren Street, Brighton, on April 1.)

Commissions are available to scientists trained in any of the following fields: bacteriology, mycology, parasitology, entomology, malacology, biology, chemistry, physiology, physics, statistics (mathematical, demographic and so forth), psychology and milk and food examination. Assignments will be in line with demonstrated ability and experience.

An applicant for the grade of assistant scientist must be a citizen of the United States, have had seven years of educational and professional training or experience, possess a certificate or diploma from an institution of recognized standing and be able to pass a physical examination given by a medical officer of the United States Public Health Service. The same requirements, plus an additional four years of training or experience, apply to those seeking the grade of senior assistant scientist.

Commissioned officers in the Regular Corps enjoy the same benefits and privileges as do officers of the Army, Navy or Marine Corps. The grade of assistant scientist is equal to that of first lieutenant in the Army. Annual pay, with allowances for dependents is $3811. A senior assistant scientist ranks with a captain of the Army and draws, with allowances for dependents $4351 a year.

United States Public Health Service officers are entitled to full medical care and hospitalization for themselves and their families, including disability retirement at three fourths base pay. They receive thirty days' annual leave with pay. Periodic promotions are based on length of service and merit. The retirement age is sixty-four.

Application forms and additional information may be obtained by writing to the Surgeon General, United States Public Health Service, Washington 25, D. C.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JANUARY 16

FRIDAY, JANUARY 17
*9:00–10:00 a.m. Changes in Biologicals and in Human Reactions. Dr. Ralph E. Wheeler. Joseph H. Pratt Diagnostic Hospital.
*10:00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

MONDAY, JANUARY 20
*12:15–1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

TUESDAY, JANUARY 21
*12:00 m. South End Medical Club. Headquarters, Boston Tuberculosis Association.
12:00 m.–1:00 p.m. Dermatological Service, Grand Rounds. Amphitheater, Dowling Building, Boston City Hospital.
*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

WEDNESDAY, JANUARY 22
*9:00–10:00 a.m. Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon. Joseph H. Pratt Diagnostic Hospital.
*11:00 a.m.–12:00 m. Medical Clinic. Amphitheater. Children's Hospital.
*12:00 m. Clinicopathological Conference. (Children's Hospital.) Amphitheater, Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.
*7:15 p.m. Graduate Seminar in Pediatrics. Children's Medical Service. Amphitheater 3A, Massachusetts General Hospital.

*Open to the medical profession.

OCTOBER 11–MAY 14. Metropolitan State Hospital. Page 398, issue of September 12.

JANUARY 14. 8:00 p.m. Harvard Medical Society. Amphitheater, Peter Bent Brigham Hospital.

JANUARY 21. South End Medical Club. Notice above.

JANUARY 22. New England Pediatric Society. Notice above.

FEBRUARY 7. American Board of Obstetrics and Gynecology. Page 44, issue of January 2.

FEBRUARY 9. National Conference on Medical Service. Page 956, issue of December 26.

FEBRUARY 13. The Clinical Importance of the Blood Type in Transfusions and in Obstetric Patients. Dr. Louis K. Diamond. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

(*Notices continued on page xvii*)